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Effect of flavonoids on bond strength of dentin adhesives: A systematic review

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Abstract--- The effectiveness of adhesive restorations depends on a durable long-term dentin bond. Due to collagen fibril denaturation, the consistency and durability of bonding to caries-affected dentin can be questioned as compared to sound dentin. Exogenous cross-linking agents have been suggested as a viable method of inhibiting MMP activity and retaining collagen within the dentin-bonded interface. Due to their strong antioxidant capacity, flavonoids are natural cross linkers that play an important role in protecting unprotected collagen fibrils inside the hybrid layer. This study aimed to evaluate the effectiveness of flavonoids incorporated dentin adhesives in improving the bond strength of composite resin. A search was performed in the electronic databases (PUBMED CENTRAL, Medline, Scopus, Lilacs, Science Direct, Google scholar and Hand Search) using search terms alone and in combination by means of PUBMED search builder upto March 2021. Also cross check of reference was done on all potentially eligible articles. Initially 47 articles were identified. 2 articles were removed because of duplicates. After title and abstract screening 27 articles were removed. After reading full texts, 4 articles were removed and finally 14 articles were included in this review for detailed analysis. The primary outcome measure was to evaluate the bond strength of resin dentin interface when flavonoids were incorporated into dentin adhesives. Meta-analysis to summarise the data from the included papers was not conducted due to the heterogeneity of the studies. As a result, only a descriptive analysis of the data has been presented. Overall the results showed that there was a significant

difference in bond strength when flavonoids were incorporated into dentin adhesives. Based on this review, within the limitation of invitro study, it may be concluded that Flavonoids can be used to improve bond strength of dentin adhesives. Flavonoids appears to interact with collagenases through hydrogen bonding and hydrophobic interactions, which cause collagenases to change their secondary structure and, as a result, inhibit MMPs. The results of this review was supported by one clinical study(Souza et al 2018).However more clinical studies are still needed.

Keywords--flavonoids, bond strength, dentin adhesives.

Introduction

In order for resin-based composite restorations to be properly sealed and retained, bonding agents are required (1). For the treatment of anterior and posterior teeth, adhesive restoration with composite resins has become the method of choice. However, due to the progressive loss of adhesive interface integrity, the long-term longevity of such restorations could be jeopardised (2). The deterioration of the dentin bond is caused by the degradation of the resin–dentin interface. Hydrolytic degradation of the resin components within the hybrid layer and collagen degradation by host-derived enzymes such as matrix metalloproteinase (MMPs) and/or cysteine cathepsins are two mechanisms for degradation (3). Collagen fibrils, elastin, and extracellular matrix (ECM) components are degraded by these enzymes, which are secreted as inactive proenzymes. These enzymes can be stimulated at a lower pH, as happens when dentin is conditioned by acid etching during the etch-and-rinse adhesive system application (4). To keep the resin-dentin bond strong, a variety of approaches to resist collagen degradation have been proposed. One promising strategy is to use MMP inhibitors as a primer before applying adhesive or as a part of dental adhesive systems, with the aim of cutting chair time (5,6). Collagen cross-linking using chemical agents with a cross-linking effect (7,8)is another method for improving the biomechanical properties of dentin and making it less susceptible to proteolytic attack(9).

Attempts to improve both collagen's resistance to enzymatic degradation and the inactivation of proteases are critical steps in improving the efficiency and durability of dental restorations(10,11). Flavonoids are a large group of organic compounds that occur naturally. Fruits, grains,seeds, tea vegetables, nuts, and wine are only a few of the plants that contain it. These are natural cross linkers that help to strengthen the resin-dentin bond(12,13). MMPs are inhibited, and collagen is preserved, resulting in immediate and delayed micro tensile bond strength (14). Many studies have been conducted to test different properties such as antimicrobial property, physico-chemical property, and mechanical property by using them as dentin pretreatments prior to adhesive system application or by integrating them into the adhesive system (15)(16). The longevity of bonded restorations is dependent on the strength of the bonds between adhesive resins and dentin. Several reports (17)(18) have been published that assess the durability of dentin bonds in vitro. Flavonoids in dentin primers and adhesives were also used in recent studies to test the bond strength of composite resin. This

present systematic review is done to evaluate the studies determining the effectiveness of flavonoids on bond stability of resin-dentin interface.

Aim

To evaluate the studies determining the effectiveness of flavonoids on bond strength of dentin adhesives.

Structured question

Does Flavonoid incorporated dentin adhesives have any effect on bond strength of resin-dentin interface?

Pico analysis

- POPULATION- Extracted Human teeth/Natural teeth
- INTERVENTION-Flavonoid incorporated dentin adhesive
- COMPARISON-Flavonoid free dentin adhesive
- OUTCOME-Bond strength
- STUDY DESIGN- In vitro/Ex Vivo studies

Null hypothesis

There is no significant difference in the bond strength between flavonoid incorporated dentin adhesive and flavonoid free dentin adhesive.

Alternate hypothesis

There is a significant difference in the bond strength between flavonoid incorporated dentin adhesive and flavonoid free dentin adhesive.

Materials and Methods

The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. PROSPERO registration number is CRD42021293721.

Search strategy and sources

For identification of studies included or considered for this review, detailed search strategies were developed for the database searched. The MEDLINE search used the combination of controlled vocabulary and free text terms.

Searched Databases

PUBMED
PUBMED Advanced Search
SCIENCE DIRECT
SCOPUS
LILACS
Google Scholar

Language

There were no language restrictions

Hand search

The following journals were hand searched

Journal of Conservative Dentistry

Journal of Dental Materials

Journal of Dentistry

Operative Dentistry

Indian Journal of Dental Research

International Journal of Adhesion & Adhesives

Egyptian Dental Journal

Eligibility criteria

Following inclusion and exclusion criteria was considering for selecting studies for this review

Inclusion criteria

- In vitro studies where flavonoid incorporated dentin adhesives were used to check bond stability of resin dentin interface
- Studies comparing conventional dentin adhesives & flavonoid incorporated dentin adhesives
- Studies that includes extracted human teeth

Exclusion criteria

The following studies were excluded:

- Reviews
- Clinical studies
- Studies that assessed the efficacy of flavonoids incorporated in composites or in other pre-treatment solutions
- Studies done on Bovine teeth
- Studies in which adhesives resin-dentin bond strength was not evaluated

Screening and selection of studies

All papers found in the databases were screened for duplicates, which were automatically eliminated. Two reviewers (M.S. and I.N) independently screened the titles. Those that were deemed relevant for this examination were printed as abstracts or full articles if the abstract was lacking. The remaining papers were ordered in full text after the abstracts were screened. The reasons for exclusion were noted during the assessment phase, and differences were reported. Following that, the reference lists of the included studies were hand-searched, and 2 additional studies with inclusion potential were screened in the same way.

Chart 1: search flow chart

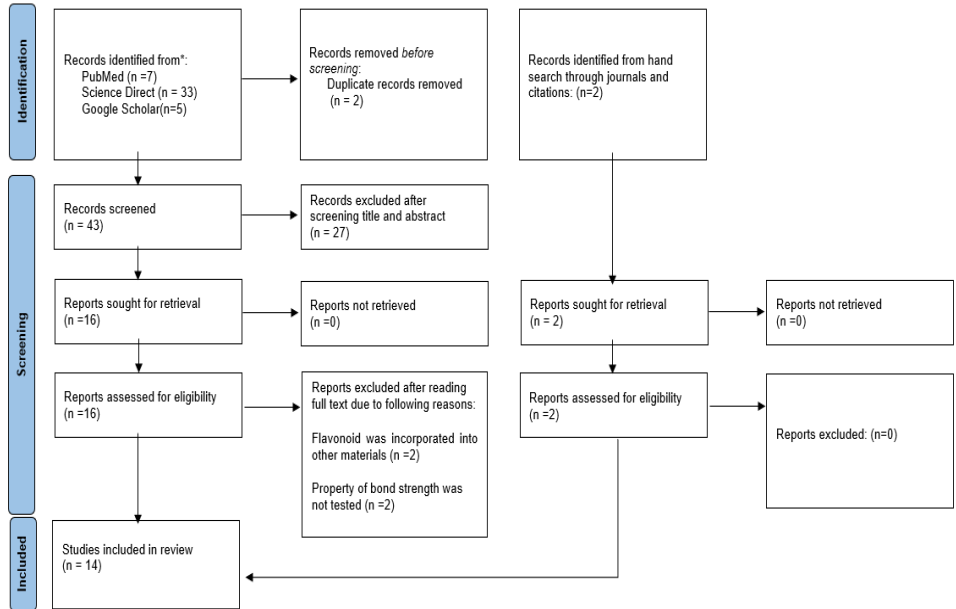


Table 1
Variables of interest

S.No.	Variables of Interest
1.	Bonding stability of resin-dentin interface

Characteristics of excluded studies

Initially 45 articles were identified through electronic search and 2 articles through hand search. 2 articles were removed because of duplicates. After title and abstract screening 27 articles were removed. After reading full texts, 4 articles were removed for the following reasons as given in table 2.

Table 2
Characteristics of excluded articles

S.No	Author	Year	Reason for exclusion
1.	Luyao et al	2019	Flavonoid was incorporated into pure ethanol

2.	Xiao et al	2000	Property of bond strength was not tested
3.	Silva et al	2020	Property of bond strength was not tested
4.	Porto et al	2018	Flavonoid was incorporated into nano composite

Results

Search results

The search identified 47 publications out of which 2 were excluded because of duplicates, 27 were excluded after reviewing the title and abstract and 4 were excluded after reading the full texts. A total of 14 publications that fulfilled all criteria for inclusion were selected.

Table 3
General information and results of the included article

S. No	Author	Study Design	Sample size	Flavonoid used	Adhesive used	Method of evaluation	Follow up	Statistical analysis	Interpretation
1.	Mendes et al 2020	Invitro study	N=50	Arabidaea chica Group-1:Control-Adper Scotchbond Multipurpose Group-2:Distilled water pretreatment Group-3:ACPA-Arabidaea chica (AC)incorporated phosphoric acid Group-4:ACW-AC incorporated aqueous solution Group-5:ACP-AC incorporated primer	Adper Scotchbond multipurpose primer solution	Microtensile bond strength using Universal testing machine(E Z test)	Immediate,6 months,1 year	Student's t test, Two way ANOVA, Chi square test, Fisher's test	ACP showed lower microtensile bond strength
2.	Yu et al			Epigallocatec	Adper	Pushout	Immediate		Epigallocatechin-3-

	2017	Invitro study	n =70	<p>Group 1- Control</p> <p>Group 2- EGCG with Adper Single Bond 2-200mg/L</p> <p>Group 3- EGCG with Single Bond 2-400mg/L</p> <p>Group 4- EGCG with Single Bond 2-600mg/L</p> <p>Group 5-SB2 + EGCG-3ME 200</p> <p>Group 6-SB2 + EGCG-3ME 400</p> <p>Group 7-SB2 + EGCG-3ME 600</p>	Single Bond 2	bond strength using Universal testing Machine(EZ-test)	e,6 months	Two way ANOVA	gallate(EGCG) modified etch and rinse adhesives showed enhanced bonding stability of intraradicular dentin-adhesive interfaces
3.	Epasinghe et al 2015	Invitro study	N=40	<p>Proanthocyanidin (PA) Group 1- Control-PA free adhesive</p> <p>Group 2- 1.0%wt PA containing adhesive</p> <p>Group 3- 2.0%wt PA containing adhesive</p> <p>Group 4- 3.0%wt PA containing adhesive</p>	Experimental adhesive	Microtensile Bond strength using Universal testing machine (Instron)	Immediate, 6 months	Two way ANOVA, Tukey's test	Bond strength of adhesives decreased with PA concentrations and ageing
4.	Khalid et al 2020	In vitro Study	N = 80	<p>Proanthocyanidin, Genipin Group 1- (Primer +Proanthocyanidin) N=20</p> <p>Group 2- (Primer + Genipin) N=20</p> <p>Group 3- (Primer +</p>	Experimental primer (Adper Single Bond 2 adhesive)	Shear bond strength using Universal testing machine	Immediate	One-way analysis of variance(ANOVA) post hoc Tukey's test	Maximum resin penetration by PA group Chemical modification with collagen crosslinkers improved bond strength at the composite resin-dentin interface

				Glutaraldehyde) N=20 Group 4- (Primer-Control) N=20					
5.	Xu et al 2020	In Vitro Study	N=90 (Human mid-coronal dentin surface s) 8 experimental primers were prepared with 5wt% and 15wt% of MDP in ethanol-aqueous solutions in combination with or without one of the following MMP inhibitors(1wt% of BAC,100microg/mL of PVPA and 15wt% of PA)	Proanthocyanidin Nine groups 6 teeth per group Group 1- Control group(self etch mode) & 8 experimental groups(Prime & rinse mode) Group 2-5% MDP Group 3- 5%MDP-BAC Group 4- 5%MDP-PVPA Group 5- 5%MDP-PA Group 6- 15%MDP Group 7- 15%MDP-BAC Group 8- 15%MDP-PVPA Group 9- 15%MDP-PA	Experimental primers	Microtensile bond strength using Bisco microtensile tester	Immediate, 1 year	Two-way ANOVA & LSD multiple comparisons test	MMP inhibitors could significantly improve short & long term dentin MTBS of self etch adhesive & resist degradation at resin-dentin interfaces.
6.	Islam et al 2014	Invitro study	N=48	Hesperidin Group 1- ClearFil SE primer-Control Group 2- 0.5% HPN Containing adhesive Group 3-	ClearFil SE Primer	Microtensile bond strength test using Universal testing machine(E Z test)	Immediate, 1 year	Two way ANOVA, Tukey's Post hoc analysis	PA group showed decreased bond strength Incorporation of 2% HPN into SE primer had a positive effect on immediate bond strength 5% HPN preserves collagen

				1%HPN containing adhesive Group 4-2%HPN containing adhesive Group 5-5%HPN containing adhesive Group 6-0.5% PA containing adhesive					morphology in hybrid layer
7.	Ghorab et al 2018	Invitro study	N=20	Hesperidin Group I- control Group II- 0.2% hesperidin incorporated Total etch adhesive Group III- 0.5% hesperidin incorporated Total etch adhesive Group IV- 1% hesperidin incorporated Total etch adhesive	Optibond Solo Plus (Total etch adhesive)	Microtensile bond strength using Universal testing machine	Immediate, 6 months	One way ANOVA, Tukey's Post hoc	The incorporation of 0.2 wt% and 0.5 wt% HPN into the dental adhesive significantly increased the immediate μ TBS ($P < 0.05$). After thermocycling, all adhesive groups revealed significant reduction in μ TBS ($p < 0.001$).
8.	Yang et al 2017	Scientific report	N=40	Quercetin Group 1- Control(Adper Single Bond 2), Group 2- Quercetin at 100 μ g/mL (Q 100) Group 3- Quercetin at 500 μ g/mL (Q 500) Group 4- Quercetin at 1000 μ g/mL (Q 1000)	Adper Single Bond 2	Microtensile bond strength using Microtensile Bond strength tester(Bisco)	Immediate, 6 months	Two way ANOVA	Quercetin-doped adhesive(500 μ g/mL) preserved its bonding properties against collagenase ageing and showed highest bond strength even after ageing.
9.	Porto et al 2021	Invitro study	N=25 per group	Quercetin, Resveratrol, Brazilian red propolis	Single Bond 2	Microtensile bond strength using	Immediate, 1 year	Student t test and ANOVA with	Dentin bonding agents with quercetin, RES, and BRP have potential

				Group 1- Single bond 2(SB2) adhesive Group 2-SB2 adhesive modified with 0.5% of Quercetin, Group 3-SB2 adhesive modified with 0.25% of Resveratrol, Group 4-SB2 adhesive modified with 0.02% of Brazilian red propolis		Microtensile bond strength tester(OM 100)		Tukey test	to increase the longevity of composite restorations by improving hybrid layer resistance
10.	Islam et al 2012	Invitro study	N=16	Hesperidin, Grape seed extract Group 1- Control Clearfil SE primer, Group 2- 0.5% HPN incorporated SE primer, Group 3- 0.5% CHX incorporated, Group 4- 0.5% GSE incorporated	ClearFil SE Primer	Microtensile bond strength using Universal testing machine(E-Z test)	Immediate	One way ANOVA Tukey post hoc	Incorporation of HPN into ClearFil SE primer has a positive influence on immediate microtensile bond strength and mechanical properties of bonded interface. GSE incorporated primer significantly decreased the bond strength.
11.	Macedo et al 2018	Invitro study	N=30	Epigallocatechin-3-gallate Group 1- Total etch adhesive Group 2-Self etch adhesive Group 3- Total etch with 0.1wt% EGCG Group 4- Total etch with 0.5wt% EGCG Group 5-Self etch with 0.1wt% EGCG	Experimental Total etch & Self etch adhesives	Microtensile bond strength using Universal testing machine (Instron)	Immediate, 6 months	Two way ANOVA and Tukey post hoc	0.5wt% EGCG increased the bond strength of etch and rinse adhesive after ageing. Dentin bond strength was reduced after ageing with addition of EGCG to self-etch adhesive

				Group 6-Self etch with 0.5wt% EGCG					
12.	Du et al 2012	Invitro study	N=20	Epigallocatechin-3-gallate Group 1- Adper single bond-control Group 2- EGCG incorporated at 100µg/ml Group 3- EGCG incorporated at 200µg/ml Group 4- EGCG incorporated at 300µg/ml	Adper single bond 2	Microtensile bond strength using Microtensile tester (Bisco)	Immediate, 6 months	ANOVA and Tukey post hoc	Immediate Bond strength of 100µg/ml & 200µg/ml EGCG incorporated groups were significantly higher compared to control. Bond strength of 3 EGCG incorporated groups were higher after 6 months
13.	Gotti et al 2015	Invitro study	N=144	Vitamin C, Vitamin E, Quercetin No. of groups=24 (based on adhesives and antioxidants used & storage period-24hrs & 6 months) Adper single bond (SB) ClearFil SE Bond (CSE) Adper Easy Bond (EB) SB Vit C CSE Vit C EB Vit C SB Vit E CSE Vit E EB Vit E SB Quercetin CSE Quercetin EB Quercetin	Adper single bond 2, ClearFil SE bond, Adper Easy bond	Microtensile bond strength using Microtensile tester (Bisco)	Immediate, 6 months	Two way ANOVA and Tukey post hoc	The performance of antioxidants changed according to adhesive system to which they were added Antioxidant doped adhesives appear to have a positive effect on adhesive interface durability- bond strength increased over time
14.	Beck et al 2020	Invitro study	N=163	Epigallocatechin-3-gallate, Proanthocyanidin, Hesperidin	ClearFil SE Primer	Shear Bond strength using Universal testing	Immediate, 6 months, 1 year	one-way ANOVA (analysis of variance)	SBS can benefit from the application of antioxidants.

				Group 1- Control group	machine		and the Tukey HSD	
				Group 2- EGCG+Distill ed water				
				Group 3- EGCG+Clear Fil Primer				
				Group 4- CHX+Distille d water				
				Group 5- CHX+ClearFil Primer				
				Group 6- PA+Distilled water				
				Group 7- PA+ClearFil Primer				
				Group 8- HPN+Distille d water				
				Group 9- HPN+ClearFil Primer				

Quality assessment

The quality assessment of included trials was undertaken independently as a part of data extraction process. Four main quality criteria were examined:

1. Method of Randomization, recorded as
 - a. Yes – Adequate as described in the text
 - b. No – Inadequate as described in the text
 - c. Unclear in the text
2. Allocation Concealment, recorded as
 - a. Yes – Adequate as described in the text
 - b. No – Inadequate as described in the text
 - c. Unclear in the text
3. Outcomes assessors blinded to intervention, recorded as
 - a. Yes – Adequate as described in the text
 - b. No – Inadequate as described in the text
 - c. Unclear in the text
4. Completeness of follow-up (was there a clear explanation for withdrawals and dropouts in each treatment group) assessed as:
 - a. Yes-Dropouts were explained
 - b. No-Dropouts were not explained
 - c. None -No Dropouts or withdrawals

Other methodological criteria examined included:

1. Presence or absence of sample size calculation

2. Comparability of groups at the start
3. Clear inclusion/ exclusion criteria

Presence / absence of estimate of measurement error. The validity and reproducibility of the method of assessment.

Risk of bias in included studies

The assessments for the four main methodological quality items are shown in table. The study was assessed to have a “High risk” of bias if it did not record a “Yes” in three or more of the four main categories, “Moderate” if two out of four categories did not record a “Yes”, and “Low” if randomization assessor blinding and completeness.

Discussion

Interpretation of results

The purpose of this review was to evaluate the efficiency of flavonoid incorporated dentin adhesives in improving the bond strength of resin-dentin interface. Fourteen in vitro studies fulfilled the criteria for being included in this review. Only in vitro studies are taken since bond strength is the variable of interest in this study.

Meta- analysis

Meta analysis is a statistical pooling of data from individual studies when the studies are similar, and is usually used in systematic reviews. A meta-analysis may provide a more accurate measure of the treatment effect overall. Meta-analysis, on the other hand, might not be sufficient in certain cases. We were unable to conduct a meta-analysis to summarise the data from the included papers due to the heterogeneity of the studies. As a result, only a descriptive analysis of the data has been presented.

Effect of bond strength based on type of flavonoid used

Flavonoids are natural cross linkers with powerful antioxidant and antiinflammatory properties. When applied to dentin, antioxidants are renowned for their ability to enhance the collagen network. They form new intramolecular and intermolecular connections in collagen, making it less susceptible to enzymatic hydrolysis. Flavonoids appears to interact with collagenases through hydrogen bonding and hydrophobic interactions, which cause collagenases to change their secondary structure and, as a result, inhibit MMPs. Also many other studies have confirmed the MMP inhibitory effect of flavonoids. The benefit of flavonoid incorporated dentin adhesive on bond strength of resin dentin interface was assessed in this study. There are various types of flavonoids that influence the bond strength of dentin adhesive.

Arrabidaea chica used as a flavonoid

Arrabidaea chica (AC) was used in one study. Mendes et al 2020 investigated the long-term bond strength of a 2.5 percent polyphenol-enriched extract of AC

incorporated into phosphoric acid and the primer of a three-step total-etch adhesive(19).They found that using AC in the primer resulted in lower bond strength values because AC changed the physical properties of the adhesive. However, using AC as a dentin pretreatment had no impact on the hybrid layer's bond strength or micro morphological characteristics.

Epigallocatechin-3-gallate (EGCG) used as a flavonoid

EGCG was used in four studies. In a study by yu et al 2017, epigallocatechin-3-gallate (EGCG) and epigallocatechin-3-O-(3-O-methyl)-gallate (EGCG-3Me) modified etch-and-rinse adhesives (Single Bond 2, SB 2) were tested for bonding stability to dentin(20). They concluded that the EGCG/EGCG-3Me modified adhesive had higher MTBS after thermocycling than SB 2, with no association with the concentration. This was explained by some studies that, EGCG inhibits MMP-9 and CT-B by binding to the catalytic site or an allosteric site of proteases, causing the enzyme to change conformation, or by chelating zinc(21).In the same way, they can inhibit the action of proteases. In comparison to EGCG, EGCG-3Me had a longer-lasting inhibitory effect on proteases. This observation was due to EGCG-3Me's higher stability. Also Macedo et al. (2018) investigated the dentin adhesion and physicochemical properties of experimental etch-and-rinse and self-etch adhesives doped with epigallocatechin-3-gallate (EGCG), and discovered that the addition of EGCG to self-etch adhesive decreased dentin-bond strength after ageing(22). Nonetheless, after ageing, 0.5 percent EGCG increased the bond strength of etch-and-rinse adhesive, while EGCG-free control adhesive had a substantial reduction.This could be clarified by a late polymerization with high antioxidant concentrations, where the photoinitiator and EGCG were in equilibrium resulting in increased cross linking.In the case of the self-etch adhesive, the thin layer of collagen revealed seems to have a slight impact on bond durability.In the same study,Immediate bond strength reduction was observed.This may be linked to the interaction between the photoinitiator and the antioxidant.Du et al. (2012) investigated the physicochemical properties of a etch and rinse dental adhesive infused with epigallocatechin-3-gallate (EGCG) in various concentrations over time and discovered that the EGCG-infused dental adhesive had a higher micro-TBS than the control(23). He came to the conclusion that dental adhesives containing 200 mg/ml EGCG could maintain the resin-dentine bond's durability.This may be because the EGCG bonds to the resin on the hybrid layer acting as MMP inhibitor and retaining the bond durability.EGCG appears to interact with collagenases through hydrogen bonding and hydrophobic interactions, which cause collagenases to change their secondary structure and, as a result, inhibit MMPs. Also many other studies have confirmed the MMPs' inhibitory effect of EGCG(24,25)

Quercetin used as a flavonoid

Quercetin was used in three studies.Yang et al 2017 evaluated the bond strength of flavonoid incorporated adhesive by developing a versatile therapeutic adhesive by incorporating quercetin, a naturally derived plant extract, into a commercial adhesive at three concentrations (100, 500, and 1000g/mL), and concluded that quercetin-doped adhesive (500g/mL) maintained its bonding properties against collagenase ageing(26). Another study investigated the bond strength of a

commercial dental adhesive modified with quercetin, resveratrol (RES), and Brazilian red propolis (BRP), and found that, unlike the control group, TBS values for all modified adhesives were preserved after 1 year in distilled water ($P > 0.05$). These results indicate that quercetin, RES, or BRP may be useful in improving hybrid layer resistance in adhesive dentistry(27). Islam et al. 2012 investigated the effect of incorporating natural cross-linkers into the primer of a self-etching adhesive on resin–dentine bond strength and found that incorporating HPN significantly increased micro-TBS, incorporating Grape seed extract(GSE) significantly decreased micro-TBS(28), and incorporating Chlorhexidine(CHX) did not show any statistically significant differences. These results show that incorporating HPN into Clearfil SE primer improved the micro-TBS and mechanical properties of the bonded interface right away. Gotti et al. (2015) investigated the effects of quercetin on dentin bonding efficiency in three commercial adhesive systems (Adper single bond 2(SB), Clearfil SE bond(CSE), and Adper Easy bond(EB)) and found that antioxidant doped adhesives retained and increased bond strength during storage for 6 to 24 months(29).

Proanthocyanidin used as a flavonoid

Four studies used Proanthocyanidin to check bond stability. Evaluation of the natural crosslinkers like proanthocyanidin, genipin, and glutaraldehyde showed that it affected shear bond strength at the composite resin-dentin interface(30). The researchers found that chemical modification with collagen crosslinkers improved bond strength at the composite resin-dentin interface. Since galloyl groups are present in PA, it strengthens collagen type I(31). It has the ability to significantly reduce endogenous enzyme activity. It also reduces the number of degrading enzyme binding sites on collagen fibres, regardless of how long it is applied(32). It also removes unbound water from collagen molecules, that prevents resin from penetrating the intertubular space(33). By crosslinking with collagen, it also helps to reduce dentin's hydrophilicity. After one year of collagenase digestion, the bond strength of PA-incorporated primer to dentin was substantially higher than PA-incorporated adhesive. PA interference with the photoinitiator will result in a reduced degree of conversion and incomplete setting of the bonding agent if it is applied to the adhesive bottle(34). This study result was similar to Epasinghe et al. (2015) study who investigated the impact of incorporating 1–3% PA into a dental adhesive on resin–dentin bond durability and found that bond strength of adhesives decreased with PA concentrations and ageing(13). The bond strength of PA-incorporated adhesive was unaffected by the type of water exposure. The addition of proanthocyanidin to a dental adhesive did not prevent the bond between the resin and the dentin from deteriorating over time. Similarly, adding 5% or more PA to an adhesive disrupted the polymerization of the resin. In the hybrid layer produced by the PA-containing adhesive, increased porosity with voids was observed, suggesting weaker polymerization of the adhesive. Also PA is a well-known antioxidant and scavenger of free radicals. When PA was used in an adhesive, it absorbed the CQ/amine photo-initiator system's free radicals and slowed the polymerization rate. This may be reason for its negative effect. On contrary Beck et al 2020 evaluated the benefit on shear bond strength (SBS) of a resin–composite to dentin when antioxidants with different biomolecular mechanisms or a known inhibitor of enzymatic activity are added to the bonding phase(35). He discovered superior

SBS in PA relative to all other agents ($p < 0.01$) and higher efficiency in both primer and solution application as compared to control after six months of immersion. After a year, both PA incorporated research groups had the most consistent results. As a result, he came to the conclusion that antioxidants would help improve the SBS.

Hesperidin used as a flavonoid

Four studies used hesperidin to check bond stability. One study investigated the effects of natural cross-linkers in a self-etch adhesive primer on immediate and long-term micro-tensile bond strengths (TBS) to dentin(36), concluding that the addition of 2% HPN to the self-etching primer improved the immediate micro-TBS and mechanical properties of the resin–dentin interfaces. After a year in artificial saliva, the 5 percent HPN group held the morphology of the collagen in the hybrid layer. Ghorab et al. (2018) investigated the adhesive properties of a condensed total-etch adhesive system containing various amounts of Hesperidin (HPN)(37), concluding that adding 0.2 wt percent and 0.5 wt percent HPN to the dental adhesive substantially increased the immediate TBS ($P < 0.05$). Thermocycling greatly decreased the TBS of 0.5 wt percent HPN integrated dental adhesives.

Self-etch vs total etch dentin adhesives

The performance of antioxidants changed according to adhesive system. Immediate and delayed bond strength was more in self etch groups. This was concluded by a study that investigated the effects of MMP inhibitor on dentin bonding efficiency in three commercial adhesive systems (Adper single bond 2(SB), Clearfil SE bond(CSE), and Adper Easy bond(EB))(38). However another study investigated the effects of a novel prime-and-rinse mode using matrix metalloproteinase (MMPs) inhibitors on dentin microtensile bond strengths (MTBS), resin-dentin interface degradations, and activity of recombinant human (rh) MMP8,-9 on dentin microtensile bond strengths(39). He found that all primers used in prime-and-rinse mode improved long-term dentin MTBS ($P < 0.05$). The smear layer functions as a physical barrier to adhesive monomer penetration. Prior phosphoric acid etching aids in increasing monomer impregnation, resulting in the creation of a hybrid layer that is merged with the dentin(40). Macedo et al. (2018) investigated the dentin adhesion and physicochemical properties of experimental etch-and-rinse and self-etch adhesives doped with epigallocatechin-3-gallate (EGCG), and discovered that the addition of EGCG to self-etch adhesive decreased dentin-bond strength after ageing. Nonetheless, after ageing, 0.5 percent EGCG increased the bond strength of etch-and-rinse adhesive. Thus the results are contradictory and inconclusive.

Summary of evidence

The aim of this systematic review was to establish whether flavonoids can be used effectively in dentin adhesives and to determine its ability in promoting retention rate of dentin adhesives. A search was performed in the electronic databases (i.e., PUBMED CENTRAL, Medline, Scopus, Lilacs, Science Direct, Google scholar and Hand Search) using search terms alone and in combination by means of PUBMED search builder upto March 2021. The search identified 47 publications out of

which 2 were excluded because of duplicates, 27 publications were excluded after reviewing the title or abstract and 4 were excluded after reviewing the full articles. A total of 14 publications fulfilled all criteria for inclusion. Efficiency of flavonoids in bond strength of resin-dentin interface was the primary outcome for evaluation.

From the 14 included studies, 12 studies showed that the flavonoid incorporated dentin adhesive showed improved bond strength compared to conventional adhesive. 2 studies showed that conventional adhesives were more effective(13,19). The maximum follow up period was two years. Arrabidaea chica, Epigallocatechin-3-gallate, Proanthocyanidin, Quercetin ,Resveratrol, Hesperidin, Genipin and Grape seed extract were the flavonoids used in these studies. Among the flavonoids, all showed positive effects in improving bond strength of resin-dentin interface except Arrabidaea chica and grape seed extract. Two studies(30,39) showed positive effect of Proanthocyanidin related to its bond stability and two studies (13,36) showed negative effect. Epigallocatechin-3-gallate and Hesperidin were used in four studies (20,22,23,28,35–37) and Quercetin was used in three studies(26,27,29). These flavonoids are also effective in preventing collagen degradation due to ageing. Based on the results of adhesive strategy, two studies (22,29) used both total etch and self etch adhesives. One study (22) showed positive effect of Total etch adhesive and another study (29) favoured Self etch adhesive. The main limitation of this review was heterogeneity in materials and methods of all included studies. Also studies included were laboratory studies which has low quality of evidence. Several aspects that could affect bond strength in clinical conditions, such as masticatory stresses, pH and temperature cycling, as well as the wet environment, which could lead to rapid deterioration of the adhesive surface, must be considered. As a result, the validity of bond strength testing to predict dental adhesive clinical performance is debatable. However the results of this review was supported by one clinical study(41). More clinical studies are still needed.

Conclusion

Within the limitations of the study, it can be concluded that Flavonoid incorporated dentin adhesives can be used as an alternative to conventional adhesives. Chemical modification of dentin adhesives with collagen crosslinkers like flavonoids can improve the bond strength of composite resin by preventing collagen degradation.

Quality of evidence

All the studies included in this review have a level of evidence 5(Oxford Centre for Evidence Based Medicine- Levels of Evidence (2009)6). All are in vitro studies, thus the level of evidence is low.

Implications for practice

Flavonoid incorporated dentin adhesive can be used efficiently in improving the bond strength of composite resin.

Implications for research

In future, research should be aimed at utilizing this flavonoid incorporated dentin adhesives in animal and human populations to exert its associations with other products.

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