Innovations

Review article

The Clinical Benefits of Triclosan in Dentistry

Dr. Sangeetha Subramanian[1*], Dr. Devapriya Appukuttan, [1]Dr. Prakash PSG[1], Dr.Aishwaraya V L[2], Dr. Jasmine Crena[3], Dr. Santhosh Venkadassalapathy[4]

[1]Professor, Department of Periodontics, S.R.M. Dental College, Ramapuram.
[2]Post-Graduate, Department of Periodontics, S.R.M. Dental College, Ramapuram.
[3]Senior lecturer, Department of Periodontics, S.R.M. Dental College, Ramapuram.
[4]Reader, Department of Periodontics, S.R.M. Dental College, Ramapuram,
Corresponding Email: sangeetha_doc@yahoo.com

Received: 11 March 2022 **Accepted:** 14 April 2022 **Published:** 30 April 2022

Abstract

Triclosan (TCS), the antimicrobial agent is incorporated into various healthcare products like dentifrices, mouthwash, hand soapsand antiseptics.In dentistry, triclosan is recommended to prevent caries, periodontal diseases,peri-implantitis and halitosis. TCS has short physiological half-life and it is rapidly absorbed, metabolized, and eliminated from the body.TCS is metabolized by phase II enzymes to glucuronide and sulfate conjugates.TCS blocks the active site of enoyl reductase enzyme in bacteria and thereby inhibit bacterial growth. TCS has prominent anti-inflammatory properties which accounts for its anti-gingivitis action.Triclosan-containing dentifrice may be beneficial for the modulation of osteo-immunoinflammatory response around implants by reducing the levels of RANKL/ OPG, which could represent a method to prevent peri-implant mucositis.Research indicated that overuse of triclosan may contribute to the development of resistant microbes.The present review about TCS highlights the dental uses of triclosan, its antimicrobial resistance, safety, adverse effects and toxicity.

Keywords: 1.*Antigingivitis, 2.Dentifrices, 3.Dental caries, 4.Mouthwash, 5.Triclosan*

Introduction

Triclosan (TCS), 5-chloro-2-(2,4-dichlorophenoxy) phenolis asynthetic, organic,nonionic,white powder that possesses functional groups for both phenol and ether. It is a broad-spectrumantimicrobial agent and hencegained vast popularity in various healthcareproducts.Triclosan is regulated by both the Food and Drug Administration(FDA) and United States Environmental Protection Agency (EPA).[1]Triclosan is taken into account as an over-the-counter medicine tobe used in hand soaps, toothpaste, deodorants, detergent, antiseptics for wound care and medical devices.TCS is used as an active ingredient in oral hygiene products in Europe and United States since 1980s and 1990srespectively.[2,3]In dentistry, triclosan is recommendedto prevent caries, gingivitis, halitosis and is also used in sutures to prevent intraoral infections after surgical procedures.

Pharmacokinetics

TCS has short physiological half-life and it is rapidly absorbed, metabolized, and eliminated from the body.[4]TCS reaches thecirculation by rapid absorption through the skin and mucous membranes of the oral cavity and alimentary tract.Plasma levels of TCS increases rapidly following the use of TCS incorporated mouth rinses or dentifrices.After swallowing a single oral dose of 4 mg of triclosan mouthwash, plasma TCS levels reaches a maximum concentration within 1 to 3 hours.The terminal plasma half-lifeafter oral exposure was 21 hours.[5]Oralrinsing with 15 ml of 0.03% TCS incorporated mouth rinse for 30 seconds twice daily resulted in total mean plasma levels of 0.26–0.33 Mm.[6]

On exposureto mouthrinsecontaining 0.03% triclosan,the average daily oral retention of triclosan was calculated to be 0.660 mg, which is 7.33% of the TCS dose applied.Dental plaque contained approximately 20.5-46.4 microgram of TCS per gram of plaque collected. Interestingly, few studies reported the retention of TCS in the oral mucosa and it was 4–13% with 0.03% TCS [6] mouth rinse and 25% with 0.2% TCS-containing toothpaste.[7]Dentifrices that contain 0.3%TCS, possibly leads to even higher oral retention.

TCS is extensively distributed in tissues and crosses the blood–brain barrier to reach the brain.[8] Triclosan has been detected in human breast milk, blood, and urine samples. Liver has been reported to have the highest concentration of TCS when various samples were analyzed after exposure to TCS.The next organ with highest concentration is adipose tissue followed by the brain with the lowest TCS concentration[8].

Metabolism of triclosan

TCS gets metabolized in the liver primarily by however a small amount of TCS was metabolized in skin. TCS is metabolized by phase II enzymes to glucuronide and sulfate conjugates. Glucuronate conjugation predominates in humans andthe mean plasma concentration for TCS-glucuronide was 220–300 μM and for TCS-sulfate was 0.028– 0.062 μM after 21 days of using an oral rinse containing 4.5 mg TCS.[8,9]A decrease in TCS cytotoxicity with a rise in glucuronidation glucuronidation and sulfonation metabolism of TCS was reported.[10]induces cytochrome P450 in rat hepatic microsomes,the enzymes responsible for its metabolism.[11]These hydrophilic conjugates of TCS reduces the bioaccumulation of TCS.

The primary mode of elimination of TCS is urinary excretion and fecal elimination is the secondary route.[12]The median excretion half-life is 11 hours after oral intake.

Mechanism of action

Triclosan is operative against both gram-positive and gram-negative bacteria. The primary site of triclosan's antimicrobial action is the bacterialcytoplasmic membrane.[2]TCSblocks lipid biosynthesis in bacteria by inhibiting the active site of enoyl reductase enzyme(ENR).This is a key enzyme required for synthesizing fatty acids to buildbacterial cell membranes. As a result, cell membranes are not properly produced and bacterial proliferation stops.Therefore, only a small TCS dose is required to inhibit bacterial growth.[13]

A single molecule of triclosan can permanently disable an ENR molecule, and hence even small dose of TCS effectively hinder bacterial growth. Triclosan impairs essential amino acid uptake at bacteriostaticconcentrations whereas it damages the cytoplasmic membrane and causes leakage of cellular contents at bactericidal concentrations

Antimicrobial resistance

Research indicated that overuse of triclosan may contribute tothe development of resistant microbes.[14]The mechanism of microbial resistance to TCScan be attributed to: (1) overproduction of targets/amplification or(2) modification of target.[2]Interestingly, the bacterial gene that produces ENR can mutate, giving rise to triclosan-resistant strains of bacteria. The membrane impermeability and efflux mechanisms account for the insusceptibility of *E. coli* isolates to TCS.[15]Additionally, overexpression of the TCS target enzyme enoyl reductase in E.coli can be attributed to the resistance. TCS exposure resulted ininduction of expression of an efflux pump in *P.aeruginosa* leading to high-level resistance to TCS andciprofloxacin. The nonsusceptibility of enoyl reductase and outer membrane permeability barrier are the factors attributed to the intrinsic resistance of *P. aeruginosa* to TCS.[16,17]TCS resistance in laboratoryexperiments hasrevealed changes in antibiotic susceptibility, however, comprehensive environmentalinvestigations have not yet clearly established any relationship between TCS usage and antibioticresistance.

Anti-inflammatory properties

TCS is a modulator of both immune and inflammatory reactions and data from in vitro and in vivo studies indicated that TCSis an immunosuppressive agent. The anti-inflammatory properties of TCS were very well established in invitro studies.TCS was also shown to suppress a wider range of inflammatory mediators including IL-1β-induced prostaglandin I2 (PGI2),arachidonic acid, cyclooxygenase-1and 2, tumor necrosis factor (TNF)α-induced PGE2, phospholipase A2 (PLA2).[18,19] Multiple inflammatory mediators induced by lipopolysaccharide like IL-1 & IL-6, interferons (IFN), and colony stimulating factor 2 were also inhibited by TCS.[13]

Mustafa et al. identified IL-1β, IFNγ, major histocompatibility complex (MHC) class II, and PGE synthase- 1, as targets of TCS in human gingival fibroblasts.[20] Moreover, in primary human oral epithelial cells, TCS attenuated LPS-induced cytokine response including IL-8, IL-1α, and TNFα and also exhibits antimicrobial response, which was mediated through microRNA (miRNA) regulation of the toll-like receptor (TLR) pathway.[21] TCS stimulated miR146a and inhibited miR155s and thereby abrogated LPS-induced TLR response. TCS reduces the capacity of natural killer lymphocytes to lyse chronic myelogenous leukemia K562 cells.[22]

An invitro study reported that when IL-1β was increased to 200 pg/ml from 50 pg/ml, 1 μg/ml of TCS blocked a significant elevation in PGE2.[23] In another study, triclosan was shown to inhibit TNF -induced PGE2 production.[24]TCS inhibited the MHC in macrophages, as well as hindered the production and secretion of proteases by human bone and fibroblastic cells when stimulated by IL-1β or TNF- α.In whole blood leukocytes, TCS downregulated the expression of NF-κB-inducing kinase and C-jun, which was responsible for the overall blunted inflammatory response to LPS.[25]

Safety

The approved concentration of TCS for topical administration and use in oral medications is 0.3 % (w/w) and 0.03 % (w/w) respectively. Triclosan at concentrations of 0.2% to 2% has antimicrobial activity and is incorporated into soaps and other consumer goods. As per FDA recommendation, up to 1% TCS is permitted for use in antiseptic washes and surgical hand scrubs.[2]

Dental uses

DeSalva, Kong Lin reviewed the toxicological information on triclosan and reported that it can be safely utilised in oral products. [26] TCS is incorporated into oral products as it is active against most of the oral bacteria and has a good record of safe use in consumer products.Studies demonstrated that the combined effect of fluoride dentifrice containing triclosan and the polyvinylmethyl ether/maleic acid (PVM/MA) copolymer had a greater uptake of TCS by enamel and buccal epithelial cells than from a dentifrice containing triclosan alone.

Colgate Total Toothpaste is one of the commercially available toothpastes and its antigingivitis effect results from the combined antimicrobial and anti-inflammatory properties of triclosan.[27]TCS, when applied intracrevicularly, improved clinical parameters of gingivitis.[28]Data revealed that the use of triclosan/ copolymer-toothpaste significantly slowed the progression of periodontitis in patients with cardiovascular disease but that it had limited influence on key subgingival periodontal pathogens in these cohorts suggesting that the clinical efficacy may be the result of a local anti-inflammatory effect.[29]In a 6-month study with the application of 0.3% triclosan/2% copolymer twice a day, a reduction in plaque deposition and bleeding as well as over a 90% reduction in anaerobic bacteria such as *Aggregatibacteractinomycetemcomitans, Fusobacterium nucleatum, and Porphyromonasgingivalis*in the gingival pockets around the implants was observed.[30]

There are numerous trials that studied the effects of triclosan dentifrice on plaque control, anti-gingivitis action, dental caries, oral malodor, plaque microflora, stain removal and periodontitis. The oral health benefits following the use of 0.3% triclosan and 2.0% PVM/MA copolymer in a fluoride base dentifrice in comparison to a placebo dentifricehas been assessed in several clinical trials (Table 1)

The combination of chitosan/collagen (1:1 v/v) and 0.1% triclosan as matrix exhibited the highest antimicrobial effect against *S. aureus*. Moreover, cytotoxicity was absent at 24-h incubation with fibroblast cells.[74] It can be potentially used to prevent infections and avoid antibiotic therapy after dental extraction and needs to be validated in clinical trials.

TCS in resin composites

The resin composites incorporated with triclosan methacrylate could greatly reduce the bacterial adhesion of *S. mutans* and biofilm formation. There is no cytotoxic effect with the use of this resin. The surface hardness and roughness of this experimental composite before and after brushing, was not significantly affected.[75]Sorption, solubility and diametral tensile strength of the material were maintained, hence it is a promising dental resin with intrinsic antibacterial action.[76]This resin composite might prevent the secondary caries along the margins of the restorations;however, should be clarified in vivo experiments for clinical application in the future.

Triclosan in Nanodentistry

In an attempt to obtain a novel drug delivery system, Pinon-segundo et aldeveloped triclosan-loaded nanoparticles by the process of emulsification-diffusion.Intrapocket drug delivery ofTCS nanoparticles were able to reduce gingival inflammationfor the treatment of periodontal disease. [77]. Chitosan based nanogel system with triclosan and flurbiprofen had anti-bacterial and anti- inflammatory activity and it was observed

that it had excellent therapeutic outcomes on experimental periodontitis in rats.[77]Triclosan when encapsulated into the dendrimer results in its solubilization and slow release of the drug with improved efficacy. Halloysite nanotubes which delivers bioactive components has been tried as drug delivery system with triclosan in dental resins for restoration. [78,79]

TCS in intracanal medication

The minimum bactericidal concentrations (MBC) of triclosan and triclosan with Gantrez® against P intermedia,F nucleatum, A naeslundii, P gingivalis, and E faecalis weredetermined by Nudera et al.[80]The MBC of triclosan wasfound to be between 12 and 94 g/mlwhereas it ranged from 0.3 to 10.4 g/ml for Gantrez®. Gantrez® increases the triclosan's bactericidal activity and was found to be effective against the five endodontic pathogens studied.TCS with or without the addition of the copolymer Gantrez might emerge as a valuable antimicrobial agent for use in endodontic treatment as an irrigating solution or intracanal medication.

TCS in sutures

Triclosan coated antibacterial sutures are effective against periopathogens like S. mutans, F. nucleatum, A. actinomycetemcomitans, P. intermedia, and P. gingivalis.Triclosan is effective in significantly reducing the bacterial adherence to suture material which can decrease the intraoral infection andmorbidity.[81]Triclosan-coated suture showed substantial reduction in biofilm formation in comparison to plain uncoated suture. This effect of triclosan has been confirmed in a meta-analysis which has demonstrated that triclosan-coated sutures significantly reduced the risk of site specific infection in clean and contaminated surgery. Interestingly, triclosan-coated Vicryl sutures did not decrease the incidence of surgical site infection in dental implant surgery.[82]Further TCS coated sutures needs to be assessed for their cost effectiveness of implementing the use of these sutures.

TCS in peri-implantitis

The regular use of atriclosan-containing dentifrice improved dental implant maintenance by reducing dental plaque and peri-implant bleeding.[83]It was found to be effective at decreasing theclinical signs of inflammation of peri-implant mucositis.[84]Studies have demonstrated the favorable value of triclosan/ fluoride toothpaste in the decline of bleeding around both teethand implants when compared to fluoride dentifrices in non-smokers.[83,84]Riberio et al indicatedthat there was an up-regulation of IL-10, an anti-inflammatory biomarker in peri-implant fluid when implant sites in non-smokers.[85]

Triclosan dentifrice modulates the host response by inhibiting proinflammatory local mediators such as IFN-γ, IL-6, PGE2 andIL-1β involved in peri-implant lesions.[25]Data from investigations performed innon-smokers, showed that OPG was significantly increased in triclosan-treated implants.Osteoclastogenesis inhibitory factor suchas bone morphogenetic protein BMP2 and BMP6were up-regulated by triclosantreatment,[25] reinforcing the hypothesis that triclosanmay interfere with the levels of specific osteo-inflammatorymediators. A triclosan-containing dentifrice may be beneficial for the modulation of osteo-immunoinflammatory responsearound implants in smokers, by reducing the levels of RANKL/OPG, which could represent a method to prevent peri-implantmucositis.[85]

Toxicity

There is a hypothesis that TCS induces the production of chloroform, a known human carcinogen. However, when toothpaste containing TCS is used, studies showed that there was no measurable quantities of

chloroform formed.[86]A correlation between increased ROS and elevated TCS concentrations in human urine samples indicated that TCS enhanced ROS production in humans.[87]TCS elevated proinflammatory cytokine expression of TNF-α and IL-6 in mouse liver.[88] Certain in vitro studies suggested that TCS promotes cancer [89]In mouse liver, TCS enhanced hepatocyte proliferation and reactive oxygen species (ROS) production thereby acting as a liver tumor promoter. [90]TCS seems to be more cytotoxic to prostate cancer compared to nonmalignant cells. [92]Conversely, data from other studies suggested that TCS may inhibit cancer development.[90,91]

Adverse effects

Triclosan affect hormones like testosterone and estrogen, and may also affect thyroid system, which regulates weight and metabolism. TCS has been regarded as an endocrine disruptor in animal studies and has shown to cause antibiotic cross-resistance. [92]The continuous use of a 0.3% triclosan toothpaste over 4 years does not have any detectable effect on thyroid function in a subset of Cardiovascular and Periodontal study population.The study emphasizes that 0.3% triclosan in toothpaste is safe and free of significant thyroid adverse effects. [93]

Bhargava and Leonard reviewed a study where 1200 human subjects participated and used toothpaste and mouth rinse/slurries containing triclosan at 0.06% to 0.6%.The blood chemistry and hematology analyses of the participants exhibited no local or systemic effects after 1 to 12 weeks of use.[94,95]

Ban of Triclosan

Several European countries have issued national consumer advisories for the use of triclosan.In December 2017, the FDA issued a final rule regarding certain OTC health-care antiseptic products including TCS.Minnesota has banned sale of TCS incorporated soaps in 2014. Canada is in the process of banning TCS from 2015. Asian countries like Korea and Japanrestrict the use of triclosan in cosmetics TCS still remains in many consumer products, including popular toothpaste. A Cochrane review study demonstrated the clear benefits of triclosan toothpaste with no serious safety concerns after three years of usage of triclosan dentifrice.[96]

Degradation of Triclosan

The occurrence of triclosan in the environment has raised a great concern as triclosan is a weak endocrine disrupting compound and can be potentially transformed into more toxic chlorinated compounds in the environment such as chlorodioxins,chlorophenol and chloroform through photo-degradation or reactionwith oxidants.[97]It is difficult to apply physical/chemical methods for TCS removal in large-scale natural environments.Manymicrobes, such as a wastewater enrichment consortium, wastewater microorganisms and soil microorganisms have proven to be effective for the biodegradation of TCS. TCS can be cometabolically degraded by several oxygenase-expressing aerobic bacteria.[98]Some of the triclosan degradation methodsare sonoelectrochemical,photoelectrocatalytic, oxidativeand electro-fenton degradation.[99]

Conclusion

TCS incorporated oral products effectively prevents many oral and periodontal diseases. The potential benefits of triclosan in dentifrice seems to outweigh the risk involved. TCS should be used judiciously to patients when indicated. In humans, TCS does not seem to affect thyroid function or carries cross antibiotic resistance. More research is required in search of an effective biomaterial for biodegradation of TCS to minimize adverse effects on the environment.

Conflict of Interest: Nil

REFERENCES

1. *Jia-Long Fang , Robin L. Stingley and Frederick A. Occurrence, Efficacy, Metabolism, and Toxicity of Triclosan. J.Environ. Sci. Health., 2010; 28 :147-71.*
2. *Gurpreet SD, Surinder K and Rama P. Triclosan: Current Status, Occurrence, Environmental Risks and Bioaccumulation Potential. Int. J. Environ. Res. Public Health, 2015; 12:5657-84*
3. *FDA. Letter to Jay Feldman of Beyond Pesticides from Steven Galson of the Federal DrugAdministration. Docket no. 2005P-0432/CP 1; FDA: Silver Spring, MD, USA, 2006.*
4. *Yueh M.F and Tukey R.H. Triclosan: a widespread environmental toxicant with many biological effects. Annu. Rev.Pharmacol.Toxicol., 2016;56:251–72.*
5. *Sandborgh-Englund G, Adolfsson-Erici M,Odham G and Ekstrand J. Pharmacokinetics of triclosan following oral ingestion in humans. J.Toxicol. Environ. Health., 2006; 69:1861-73.*
6. *Lin Y. J. Buccal absorption of triclosan following topical mouthrinse application. Am J Dent, 2000;13:215–17.*
7. *Weatherly L. M and Goose J. A.Triclosan exposure, transformation, and human health effects. J. Toxi. Environ. Health Part B, 2017; 20 :447-69*
8. *Geens T, Neels H, andCovaci A., Distribution of bisphenol-A, triclosan and n-nonylphenol in human adipose tissue, liver and brain. Chemosphere, 2012; 87:796–802.*
9. *Arbuckle T.E, Marro L, Davis K, Fisher M, Ayotte P, Bélanger P, Dumas P, LeBlanc A, Bérubé R, Gaudreau É and Provencher G. Exposure tofree and conjugated forms of bisphenol A and triclosan among pregnant women in the MIREC cohort. Environ. Health Perspect., 2015;123:277–84*
10. *Wu Y., Chitranshi P, Loukotkova L,Da Costa, F. A. Beland, J. Zhang, and J. L. Fang. Cytochrome P450-mediated metabolism of triclosan attenuates its cytotoxicity in hepatic cells. Arch. Toxicol., 2017; 91:2405–23.*
11. *Hanioka N, Jinno H, Nishimura T and Ando M. 2,4,4'-trichloro-2'-hydroxydiphenyl ether on cytochrome P450 enzymes in the rat liver. Chemosphere, 1997;34:719–30.*
12. *Bagley D. M., and Y. J. Lin. Clinical evidence for the lack of triclosan accumulation from daily use in dentifrices. Am J Dent, 2000; 13:148–152.*
13. *Alfhili M.A, and Lee M.H.Triclosan:An Update on Biochemical and Molecular Mechanism. Oxidat. Med. Cell. Long., 2019;1607304: 1-28*
14. *Sanchez P, Moreno E, and Martinez J.L.The biocide triclosan selects Stenotrophomonas maltophiliamutants that overproduce the SmeDEF multidrug efflux pump. Antimicrob. Agents.Chemother.,2005; 49: 781–82*
15. *Gomez-Escalada M, Maillard J. Y, Russell A.D. Effects of triclosan-sensitive and resistant strains of Gram-negative bacteria. Soc. Appl.Microbiol., 2001; 30:9–12.*
16. *Chuanchuen R, Beinlich K, Hoang T.T, Becher A, Karkhoff-Schweizer R.R and Schweizer HP. Cross-resistance between triclosan and antibiotics in Pseudomonas aeruginosa is mediated by multidrug efflux pumps: exposure of a susceptible mutant strain to triclosan selects nfxB mutants overexpressing MexCD-OprJ. Antimicrob. Agents.Chemother, 2001;45:428-32.*
17. *Heath R.J, White S.W and Rock C.O. Lipid biosynthesis as a target for antibacterial agents. Prog. Lipid Res,2001; 40:467–97.*
18. *Gaffar A, Scherl D, Afflitto J, and Coleman E. J.The effect of triclosan on mediators of gingival inflammation. J. Clin. Periodontol., 1995; 22:480– 84.*

19. *Modéer T, Bengisson A, and Rölla G.Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 in vitro.J. Clin.Periodontol., 1996; 23: 927–33.*
20. *Mustafa M, Wondimu B, Yucel-Lindberg T, Kats- Hallstrom A. T, Jonsson A. S, and Modeer T. Triclosan reduces microsomal prostaglandin E synthase-1 expression in human gingival fibroblasts. J. Clin.Periodontol., 2005;32:6–11.*
21. *Wallet M. A, Calderon N. L and Alonso T. R. Triclosan alters antimicrobial and inflammatory responses of epithelial cells. Oral Diseases, 2013; 19:296–302.*
22. *Udoji F, Martin T, Etherton R, Whalen M. M. Immunosuppressive effects of triclosan, nonylphenol, and DDT on human natural killer cells in vitro. J.Immunotoxicol., 2010;7:205–12*
23. *Modeer T, Bengtsson A and Rolla F.Triclosan reduces prostaglandin biosynthesisin human gingival fibroblasts challenged with interleukin-1 in vitro. J. Clin.Periodontol., 1996;23: 927–33*
24. *Mustafa M, Wondimu B, Ibrahim M and Modeer T. Effect of triclosan on interleukin-1β production in human gingival fibroblasts challenged with tumor necrosis factor. Eur. J. Oral. Sci.,1998;106:637–43.*
25. *Barros S.P, Wirojchanasak S, Barrow D. A, Panagakos F. S, Devizio W, Offenbacher S. Triclosan inhibition of acute and chronic inflammatory gene pathways. J. Clin.Periodontol., 2010; 37: 412–18.*
26. *DeSalva S. J, Kong B. M, Lin Y. J. Triclosan: A safety profile. Am. J. Dent., 1989; 2:185–196.*
27. *Panagakos F. S, Volpe A. R, Petrone M. E, DeVizio W, Davies R. M andProskin H. M. Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of the clinical benefits of a triclosan/copolymer/fluoride dentifrice. J. Clin. Dent., 2005;16 Suppl: S1-19.*
28. *Suresh D. K, Vandana K. L, and Mehta D. S. Intracrevicular application of 0.3% Flurbiprofen gel and 0.3% Triclosan gel as anti-inflammatory agent. A comparative clinical study. Indian J. Dent. Res., 2001; 12:105–12.*
29. *Seymour G. J, Palmer J. E, Leishman S. J, Do H. L, Westerman B and Carle A.D.Influence of a triclosan toothpaste on periodontopathic bacteria and periodontitis progression in cardiovascular patients: a randomized controlled trial. J. Periodontal. Res., 2017;52:61-73.*
30. *Sreenivasan P. K, Vered Y, Zini A, Mann J, Kolog H and Steinberg D. A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. J. Clin.Periodontol., 2011 ;38:33-42.*
31. *Garcia-Godoy F, Garcia-Godoy F, DeVizio W, Volpe A. R, Ferlauto R. J and Miller J. M. Effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A 7-month clinical study. Am. J. Dent., 1990; 3:S15–S26, .*
32. *Cubells A. B, Dalmau L. B, Petrone M. E, Chaknis P and Volpe A. R: The effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A six-month clinical study. J. Clin. Dent., 1991; 2:63–69.*
33. *Deasy M. J, Singh S. M, Rustogi K. N, Petrone D. M, Battista G, Petrone M. E. and Voople A.R Effect of a dentifrice containing triclosan and a copolymer on plaque formation and gingivitis. Clin. Prev. Dent.,1991;13:12–19.*
34. *Mankodi S, Walker C, Conforti N, DeVizio W, McCool J. J and Volpe A. R. Clinical effect of a triclosan-containing dentifrice on plaque and gingivitis: A six-month study. Clin. Prev. Dent., 1992;14:4–10*
35. *Denepitiya J. L, Fine D, Singh S, DeVizio W, Volpe AR and Person P: Effect upon plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: A 6-month clinical study. Am. J. Dent., 1992; 5:307–11.*
36. *Bolden T. E, Zambon J. J, Sowinski J, Ayad F, McCool J, Volpe A. R. DeVizio W.The clinical effect of a dentifrice containing triclosan and a copolymer in a sodium fluoride/silica base on plaque formation and gingivitis: A sixmonth clinical study. J. Clin. Dent., 1992;4:125–31.*

37. *Palomo F, Wantland L, Sanchez A, Volpe A. R, McCool J. J and DeVizio W: The effect of three commercially available dentifrices containing triclosan on supragingival plaque formation and gingivitis: A six-month clinical study. Int. Dent.J. , 1994; 44:75–81.*
38. *Triratana T, Tuongratanaphan S, Kraivaphan P, Rustogi K. N and Volpe A. R.The effect on established plaque formation and gingivitis of a triclosan/ copolymer/fluoride dentifrice: A six-month clinical study. J. Dent. Assoc. Thailand, 1993;43:19–28.*
39. *Lindhe J, Rosling B, Socransky S. S, Volpe A. R: The effect of a triclosan containing dentifrice on established plaque and gingivitis. J. Clin.Periodontol., 1993;20:327–334.*
40. *Deyu H, Jincai Z, Wan H, Zhang Y, Volpe A. R and Petrone M. E. Efficacy of triclosan/copolymer dentifrice in the control of plaque and gingivitis. A six-month clinical study. W.C.J.S., 1997; 11:332–35.*
41. *Allen D. R, Battista G. W, Petrone D. M, Petrone M. E, Chaknis P andDeVizio W. The clinical efficacy of Colgate total plus whitening toothpaste containing a special grade of silica and Colgate total fresh stripe toothpaste in the control of plaque and gingivitis. A six-month clinical study. J. Clin. Dent., 2002; 13:59–64.*
42. *Mankodi S, Lopez M, Smith I, Petrone D, Petrone ME, Chaknis P and Proskin H. M. Comparison of two dentifrices with respect to efficacy for the control of plaque gingivitis, and with respect to extrinsictooth staining. A six-month clinical study on adults. J. Clin. Dent., 2002;13:228–33.*
43. *Triratana T, Rustogi K. N, Volpe A. R, DeVizio W, Petrone M and Giniger M. Clinical effect of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. A six-month clinical study. J.A.D.A., 2002; 133:219–25.*
44. *Schiff T, Cohen S, Volpe A. R and Petrone M. E: Effects of two fluoride dentifricescontaining triclosan and a copolymer on calculus formation. Am. J. Dent., 1990; 3:S43–S45.*
45. *Lobene R. R, Battista G. W, Petrone D. M, Volpe A. R and Petrone M. E. Clinical efficacy of an anticalculus fluoride dentifrice containing triclosan and a copolymer: A 6-month study. Am. J. Dent.,1991;4:83–85.*
46. *Volpe A. R, Schiff T. J, Cohen S, Petrone M. E and Petrone D. Clinical comparison of the anticalculus efficacy of two triclosan-containing dentifrices. J. Clin. Dent., 1992; 3:93–95.*
47. *Bánóczy J, Sari K, Schiff T, Petrone M, Davies R and Volpe A. R: Anticalculus efficacy of three dentifrices. Am. J. Dent., 1995;8:205–08.*
48. *Allen D, Battista G. W, Petrone D. M, Petrone M. E, DeVizio W and Volpe A. R. A clinical study to compare the anticalculus effect of three dentifrice formulations. J. Clin. Dent.,2002;13:69–72.*
49. *Sowinski J. A, Battista G. W, Petrone D. M, Petrone M. E, DeVizio W and Volpe A. R. A clinical study to assess the anticalculus efficacy of a new dentifrice containing a special grade of silica (Colgate Total Plus Whitening Toothpaste). A clinical trial on adults. J. Clin. Dent., 2002; 13:65–68.*
50. *Sielski C, Berta R. L, Petrone M. E, Chaknis P, DeVizio W, Volpe AR and Proskin H. M et al. A study to access the tooth whitening efficacy of a new dentifrice formulation variant containing a special grade of silica. A six-week study on adults. J. Clin. Dent., 2002; 13:77–81.*
51. *Ayad F, Khalaf A, Chaknis P, Petrone M. E, DeVizio W, Volpe AR and Proski H. M. Clinical efficacy of a new tooth whitening dentifrice. J. Clin. Dent.,2002 ;13:82–85,*
52. *Singh S, Mankodi S, Chaknis P, Petrone M. E, DeVizio W, Volpe A. R and Proskin H. M: The clinical efficacy of a new tooth whitening dentifrice formulation.A six-month study in adults. J. Clin. Dent.,2002;13:86–90,*
53. *Nathoo S, Petrone M. E, DeVizio W, Chaknis P and Volpe AR: A six-week study to compare the stain removal efficacy of three dentifrices. J. Clin. Dent., 2002; 13:91–94.*
54. *Hawley G. M, Hamilton F. A, Worthington H. V, Davies R. M, Holloway P. T, Davies T. G and Blinkhorn A. S. A 30-month study investigating the effect of adding triclosan/copolymer to a fluoride dentifrice. Caries. Res., 1995; 29:163–67.*

55. *Feller R, Kiger R.D, Triol C. W, Sintes J. L, Garcia L, Petrone M. E, Volpe A. R and Proskin H. M. Comparison of the clinical anti-caries efficacy of an 1100 NaF silica-based dentifrice containing triclosan and a copolymer to an 1100 NaF silica-based dentifrice without those additional agents: A study on adults in California. J. Clin. Dent., 1996;7:85–89.*
56. *Mann J, Karniel C, Triol C. W, Sintes J. L, Garcia L, Petrone M. E, Volpe A. R and Proskin H. M. Comparison of the clinical anti-caries efficacy of a 1500 NaF silica-based dentifrice containing triclosan and a copolymer to a 1500 NaF silica-based dentifrice without those additional agents: A study on adultsin Israel. J. Clin. Dent., 1996; 7:90–95.*
57. *Mann J, Vered Y, Babalof I, Sintes J, Petrone M. E, Volpe A. R. Stewart B, De Vizio W, McCool J. J and Proskin. The comparative anticaries efficacy of a dentifrice containing 0.3% triclosan and 2.0% copolymer in a 0.243% sodium fluoride/silica base and a dentifrice containing 0.243% sodium fluoride/silica base. A two year coronal caries clinical trial on adults in Israel. J. Clin. Dent., 2001;12:71–76.*
58. *Sharma N. C, Galustians J. H, Qaquish J, Galustians A, Rustogi K. N, PetroneM. E, Chaknis P, Gracia L, Volpe A. R and Proskin H. M. The clinical effectiveness of a dentifrice containing triclosan and a copolymer for controlling breath odor measure organoleptically twelve hours after tooth brushing. J. Clin. Dent.,1999;10:131–34.*
59. *Niles H. P, Vaquez J, Rustogi K. N, Williams M, Gaffar A andProskin H. M: The clinical effectiveness of dentifrice containing triclosan and a copolymer for providing long-term control of breath odor measures chromatographically.J. Clin. Dent.,199910:135–38.*
60. *Sharma N. C, Galustians H. J, Qaqish J, Galustians A, Petrone M. E, RustogiK. N, Rustogi K. N, Zhang Y. P, DeVizio W and Volpe A. R. The clinical efficacy of Colgate Total plus whitening toothpaste containing a special grade of silica and Colgate Total Toothpaste for controlling breath odor twelve hours aftertooth brushing. A single-use clinical study. J. Clin. Dent.,2002;13:73–76.*
61. *Hu D, Zhang Y, Volpe A, DeVizio W and Giniger M. Clinical effectiveness of a triclosan/copolymer/sodium fluoride dentifrice in controlling oral malodor: A three-week clinical trial. Oral. Dis., 2005; 11:51–53.*
62. *Rosling B, Wannfors B, Volpe A. R, Furuichi Y, Ramberg P andLindhe J. The use of triclosan/copolymer dentifrice may retard the progression of periodontitis. J. Clin.Periodontol.,1997;24:873–80*
63. *Rosling B, Dahlen G, Volpe A, Furuichi Y, Ramberg P and Lindhe J. Effect of triclosan on the subgingival microbiota of periodontitis-susceptible subjects.J. Clin.Periodontol., 1997; 24:881–87.*
64. *Furuichi Y, Ramberg P, Krok L andLindhe J. Short-term effects of triclosan on healing following subgingival scaling. A two-week clinical study. J. Clin.Periodontol.,1997;24:777–82.*
65. *Ellwood R. P, Worthington H. V, Blinkhorn A. S. B, Volpe A. R and Davies R. M. Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. J.Clin.Periodontol.,1998;26:363–367.*
66. *Furuichi Y, Rosling B, Volpe A. R andLindhe J: The effect of a triclosan/copolymer dentifrice on healing after non-surgical treatment of recurrent periodontitis. J. Clin.Periodontol., 1999; 26:63–66.*
67. *Cullian M. P, Westerman B, Hanlet S. M, Palmer J. E, Faddy M. J and Seymour G. J.The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. J. Clin.Periodontol., 2003; 30:414–19.*
68. *Kerdvongbundit V, Wikesjo U. M. E. Effect of triclosan on healing following non-surgical periodontal therapy in smokers. A two-year clinical study. J. Clin.Periodontol.,2003;30: 1024–34.*
69. *Zambon J. J, Reynolds H. S, Dunford R. G and Bonta C. Y. Effect of a triclosan/copolymer/fluoride dentifrice on the oral microflora. Am. J. Dent., 1990; 3:S27–S34.*
70. *Bonta Y, Reynolds H. S, Dunford R. G andZambon J.J. Long term effect of a triclosan/copolymer dentifrice on oral microflora. J. Dent. Res., 1992;71:557.*

71. *Walker C, Borden L. C, Zambon J. J, Bonta C. Y, DeVizio W and Volpe A. R.The effects of a 0.3% triclosan-containing dentifrice on the microbial composition of supragingival plaque. J. Clin. Periodontol., 1994; 21:334–41.*
72. *Zambon J. J, Reynolds H. S, Dunford R. G, DeVizio W, Volpe A. R, Berta R, Tempro J. P and Bonta Y. Microbial alterations in supragingival dental plaque in response to a triclosan-containing dentifrice. OralMicrob. Immunol., 1995;10:247–55.*
73. *Fine DH, Furgang D, Bonta Y, DeVizio W, Volpe AR, Reynolds H, Reynolds H, Zambon J. J and Dunford R. G.Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and on current oral microflora monitoring. Am. J. Dent., 1998;11:259–70*
74. *Villanueva-Ornelas G. E, Nunez-Anita R. E, Arenas-Arrocena M. C, Luevano-Colmenero G. H, Acosta-Torres L. S. Biocidal and bioresorbable chitosan/triclosan/collagen matrixes. Innovation, 2019; 5:e1.*
75. *de Paula A. B, Taparelli J. R and Alonso R. C. B.Innocentini-Mei LH, Puppin-Rontani RM. Synthesis and application of triclosan methacrylate monomer in resin composites. Clin. Oral.Investig., 2019;23:965-74.*
76. *Piñón-Segundo E, Ganem-Quintanar A, Alonso-Pérez V andQuintanar-Guerrero D. Preparation and characterization of triclosan nanoparticles for periodontal treatment. Int. J. Pharm., 2005;27:217-232.*
77. *Aminu N, Chan S. Y, Yam M. F, Toh S. M. A dual-action chitosan-based nanogel system of triclosan and flurbiprofen for localised treatment of periodontitis. Int. J. Pharm., 2019;30:118659.*
78. *Degrazia F.W, Leitune V.C.B, Takimi A.S, Collares F.M, Sauro S. Physicochemical and Bioactive Properties of Innovative Resin-Based Materials Containing Functional Halloysite Nanotubes Fillers, Dent. Mater., 2016; 32: 1133–43.*
79. *Degrazia F.W, Genari B, Leitune V. C. B, Arthur R. A, Luxan, Samuel S. A, Collares F. M and Sauro S. Polymerisation, Antibacterial and Bioactivity Properties of Experimental Orthodontic Adhesives Containing Triclosan-Loaded Halloysite Nanotubes.J. Dent., 2018; 69: 77–82.*
80. *Nudera W. J, Fayad M. I, Johnson B. R, Zhu M, Wenckus C. S, Begole EA and Wu C. D. Antimicrobial effect of triclosan and triclosan with Gantrez on five common endodontic pathogens. J.Endod., 2007;33:1239-42.*
81. *Sethi K. S, Karde P. A and Joshi C. P. Comparative evaluation of sutures coated with triclosan and chlorhexidine for oral biofilm inhibition potential and antimicrobial activity against periodontal pathogens: An in vitro study. Indian J. Dent. Res., 2016;27:535-39.*
82. *Ahmed I, Boulton AJ, Rizvi S, Carlos W, Dickenson E, Smith N. A and Reed M. The use of triclosan-coated sutures to prevent surgical site infections: a systematic review and meta-analysis of the literature. B.M.J. Open 2019;9:e029727.*
83. *Sreenivasan PK, Vered Y, Zini A, Mann J, Kolog H, Steinberg D, Zambon J. J, Haraszthy V. I, da Silva M. P and De Vizio W. A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. J. Clin.Periodontol., 2011;38:33–42.*
84. *Ramberg P, Lindhe J, Botticelli D and Botticelli A. The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. J. Clin. Dent., 2009;20:103–07.*
85. *Ribeiro F. V, Casati M. Z, Casarin R. C, Corrêa M. G, Cirano F. R, Negri B. M and Pimentel S. Impact of a triclosan-containing toothpaste during the progression of experimental peri-implant mucositis: Clinical parameters and local pattern of osteo-immunoinflammatory mediators in peri-implant fluid. J.Periodontol., 2018;89:203–12*
86. *Hao Z, Parker B, Knapp M. In vitro stability of triclosan in dentifrice under simulated use condition. Int. J.Cosmet. Sci., 2007;29:353–59.*
87. *Lv Y,Rui C, Dai Y, Pang Q, Li Y, Fan R and Lu S. Exposure of children to BPA through dust and the association of urinary BPA and triclosan with oxidative stress in Guangzhou, China. Environ. Sci. Process Impacts, 2016;18:1492–99.*

88. *Yueh M. F, Taniguchi K, Chen S, R. Evans R M, Hammock B. D, Karin. M and Tukey R. H.The commonlyused antimicrobial additive triclosan is a liver tumor promoter.Proc. Natl. Acad. Sci., U S A, 2014; 111:17200–205.*
89. *Kim, J. Y, Yi B. R, Go R. E, Hwang K. A, Nam K. H, and Cho K.C. Methoxychlor and triclosan stimulates ovarian cancer growth by regulating cell cycle- and apoptosis-related genes via an estrogen receptor-dependent pathway. Environ.Toxicol.Pharmacol., 2014; 37:1264–74.*
90. *Sadowski M. C, Pouwer R. H, Gunter J. H, A, Lubik A. A, Quinn R. J and Nelson C.C. The fatty acid synthase inhibitor triclosan: Repurposing an anti-microbial agent for targeting prostate cancer. Oncotarget., 2014;5:9362–81*
91. *Deepa, P. R., Vandhana S, Jayanthi U, and Krishnakumar S.Therapeutic and toxicologic evaluation of anti-lipogenic agents in cancer cells compared with non-neoplastic cells. Basic Clin.Pharmacol.Toxicol., 2012;110:494–503.*
92. *Yazdankhah S. P,Scheie A. A, Høiby E. A, Lunestad B. T, Heir E, Fotland T. Ø,Naterstad K and Kruse H. Triclosan and antimicrobial resistance in bacteria: an overview. Microb. Drug. Resist., 2006;12: 83–90.*
93. *Cullinan M. P, Palmer J. E, Carle A. D, West M. J and Seymour GJ. Long term use of triclosan toothpaste and thyroid function. Sci. Total. Environ., 2012;416:75-79.*
94. *Bhargava H. N and Leonard P. A. Triclosan: applications and safety. Am J Infect Control,1996;24:209–18.*
95. *Jones R. D, Jampani H. B, Newman J. L and Lee A. S. Triclosan: a review of effectiveness and safety in health care settings. Amer. J. Inf. Cont., 2000;28:184-96.*
96. *Riley P and Lamont T. Triclosan/copolymer containing toothpastes for oral health. Coch. Dat. Syst. Rev., 2013;12:CD010514.*
97. *Latch D. E,Packer J. L,Stender B. L,VanOverbeke J,Arnold W. A and McNeill K.Aqueous photochemistry of triclosan: formation of 2,4-dichlorophenol, 2,8-dichlorodibenzo-p-dioxin, and oligomerization products.Environ.Toxicol. Chem., 2005; 24:517-25.*
98. *Lee DG and Chu KH. Effects of growth substrate on triclosan biodegradation potential of oxygenase-expressing bacteria. Chemosphere, 2013 ;93:1904-11.*
99. *Liu H, Cao X, Liu G, Wang Y, Zhang N, Li T and Tough R. Photoelectrocatalytic degradation of triclosan on TiO2 nanotube arrays and toxicity change. Chemosphere, 2013;93:160-65.*

TABLES

Table 1. Oral health benefits of triclosan dentifrice

Effects	Clinical trials	Duration of study	Parameters/ Indices	Effect of triclosan vs Placebo
Plaque control	13 independent and double-blind [31-46]	6 months	Quigley-Hein Plaque Index	26% efficacy
			Plaque Severity Index	48% efficacy
Anti-gingivitis	13 independent and double-blind [31-46]	6 months	The Löe-Silness Gingivitis Index	25% efficacy
			Gingivitis Severity Index.	59% efficacy
Anti-calculus	6 independent and double-blind [44-49]	2-6 months	Volpe-Manhold Calculus Index	40% efficacy
Stain removal and	5 independent and	6 weeks to 6	Lobene Stain index	Stain area 44% to 50% and

whitening	double-blind [50-53,34]	months		Stain Intensity 45% to 49% lower than placebo
Anticaries efficacy	4 independent and double-blind [54-57]	30 to 36 months	DFT and DFS scores	statistically "at least as good as the placebo dentifrice
Oral malodour	4 independent and double-blind [58-61]	12 hours	Total and VSC-producing bacteria counts	TCS reduces the number of oral bacteria as well as VSC-producing bacteria.
Periodontitis	7 independent and double-blind [62-68]	24-36 months	attachment loss, bleeding on probing.	TCS significantly reduced attachment loss, bleeding on probing, and the recurrence of periodontal disease
Microflora associated with dental plaque	five independent and double-blind [69-73]	6-12 months	Development of pathogenic, opportunistic, or resistant oral microorganisms	No development of pathogenic, opportunistic, or resistant oral microorganisms with TCS use