



Elucidating The Effect Of Triclosan On Gut Microflora And Spread Of Antibiotic Cross-Resistance

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Abstract:

Many consumer items, including soap, mouthwash, shower gels, hand-wash, shampoo, deodorants, and antibacterial lotions, contain TCS. TCS is environmentally resistant and persistent due to its aromatic character and significant chlorination. One of the manufactured antimicrobials that is persistent in the environment and a major cause for concern is triclosan. When various species are exposed to TCS, cross-resistance—that is, resistance to TCS followed by resistance to antibiotics—develops. Exposure to TCS can result in a number of negative effects, including endocrine disruption, liver carcinogenesis, liver fibrosis, and antibiotic resistance. Low-dose exposure to TCS exacerbates colon inflammation and colon carcinogenesis linked to the development of colitis, indicating negative consequences of TCS exposure on gut health. Alpha diversity in the gut microbiota of children who were fed breast milk containing TCS was lower than that of children whose TCS levels were undetectable. Children who were fed breast milk containing TCS also showed modulation of abundant species.

Keywords: antibiotic resistance, cross-resistance, efflux pumps, gut microbiome, triclosan

Introduction

This compound, which was first used as an antibacterial medication in the early 1970s, has both phenolic and aromatic chlorine groups. TCS was first thought to have a non-polar nature, strong protonophore properties, and action similar to that of alcohol. Cloxifenolium, Ster-Zac, Kopsan, Irgasan® DP300, Lexol 300, and Irgasan® PG60 are TCS commercial names that are often used [1,72]. A little earlier, TCS made claims about its anti-fungal and antibacterial properties. It was demonstrated that TCS prevented gingivitis in Colgate toothpaste [47]. TCS was later added to the formulation of other consumer goods, including soap, mouthwash, shower gels, hand-wash, shampoo, deodorants, and antibacterial treatments for acne. In order to inhibit microbiological development, TCS is applied to plastic products such as conveyor belts, ice tubings, heating, ventilation, clothes, kitchenware, sealants, and toys. This is because it confers hydrophobicity and thermostability [3,16,20,56,74,76]. It is a chlorinated bisphenol that shares structural similarities with thyroid hormones, dioxins, bisphenol A, and polychlorinated biphenyl. TCS is environmentally resistant and persistent due to its aromatic character and significant chlorination [79].

Table 1: Showing producers of Triclosan with their country. (Source: Shrestha, P and Zhang, Y, et. al., 2020.)

S.no.	Producers of Triclosan	Country
1.	BASF	USA
2.	Vivimed Labs	India
3.	Kumar Organic	India
4.	Dev Impex	India
5.	Spectrum Chemical	USA
6.	Xian Medihealth	China
7.	Pierre Fabre Dermo Cosmetique	French
8.	Salicylates and Chemicals	India
9.	Buntech- Tecnologia em Insumos	Brazil
10.	Sino Lion	USA

In addition to antibiotics, manufactured antimicrobials are widely used in homes, the surrounding environment, and hospitals primarily for disinfection and sanitation [11]. One of the manufactured antimicrobials that is persistent in the environment and a major cause for concern is triclosan. In the past, the term "antimicrobial" was used to describe a wide range of substances, including antibiotics, that inhibit or kill microbes [11, 39]. Antibiotics are substances generated from microorganisms that are used to treat microbial infections in various eukaryotes, including as ciprofloxacin, erythromycin, and tetracycline. TCS interacts with physiological targets at low masses, which results in a variety of resistance mechanisms [9,13,14]. These pathways occasionally carry TCS resistance while also transmitting resistance to other antibiotic classes. In some species, cross-resistance—that is, resistance to TCS followed by resistance to antibiotics—occurs as a result of TCS exposure [11]. It was discovered that TCS promotes the evolution of efflux pumps in a variety of bacterial strains [16, 56]. Previous research have shown that exposure to TCS can result in a number of negative effects, including endocrine disruption, liver carcinogenesis, liver fibrosis, and antibiotic resistance [79].

Low-dose exposure to TCS exacerbates colon inflammation and colon carcinogenesis linked to the development of colitis, indicating negative consequences of TCS exposure on gut health [78]. TCS exposure changes the gut microbiota, however in models without gut microbiota or TLR4-1 (Toll-like receptor 4), a key regulator of host microbiome interaction that aids in the pro-inflammatory effects of the gut microbiota, the induction of colonic inflammation fails. According to reports, children who were fed breast milk containing TCS had a lower alpha diversity in their gut microbiota than children whose TCS levels were undetectable. Children who were fed breast milk containing TCS also showed modulation of abundant species [10]. Another human study found that regular use of toothpaste containing TCS increased the relative prevalence of antibiotic-resistant *Proteobacteria species* in both adults and infants with high urine TCS concentrations. Due to contradictory findings that do not show a substantial effect of TCS exposure on the human gut flora, recognition is required [55].

Mechanism of action

Antibiotic resistance is having a potentially disastrous effect on a global scale, which is impeding the effectiveness of the antibiotic era in combating infections and infectious diseases [1, 6, 49]. Two major issues are brought about by an increase in medication resistance: treatment failures and harm to both individuals and society. Because resistant germs proliferate and infect people, it could be lethal for individuals [32]. There are the typical resistance mechanisms that are encountered.

Enzyme-mediated drug inactivation: This common kind of resistance mechanism is acquired by naturally occurring antibiotics. Antibiotics of natural origin, such as β -lactams, are deactivated by the hydrolysis of β -lactamases, while aminoglycosides are deactivated by changes made to their individual enzymes, such as phosphorylation, acetylation, or adenylation. By being present on a plasmid containing another gene, their corresponding coding genes may also exhibit resistance properties. The organisms that produce the antibiotics for their own defense are an essential supply of these inactivating enzymes [48].

Table 2: Showing some inactivating enzymes and their respective enzymes with their class. (Source: Nikaido, H. 2009.)

S.no.	Class	Antibiotics	Enzymes
1.	Aminoglycosides	Kanamycin Tobramycin Amikacin	- Aminoglycoside phosphoryltransferase (APH) - Aminoglycoside acetyltransferase (AAC) - Aminoglycoside adenylyltransferase or nucleotidyltransferase
2.	β -lactams	Penicillins Cephalosporins Carbapenems	β-lactamases

Gene accession by other species for certain target proteins that are less vulnerable: Sequencing the target sites of the genes that code for penicillin in *Streptococcus pneumonia* and *S. aureus*, which were producing resistance to both penicillin and methicillin, revealed that mosaic proteins were the ones that were produced in other species [64].

Avoiding the target: Since vancomycin binds to its substrate, a pentapeptide sugar connected to lipid, it has an unusual mode. The normal intestinal tract flora of *Enterococci* is the main source of resistance. D-lactic acid was added to the end region of pentapeptide to prevent it from binding to vancomycin [15].

Changes in the target protein by mutation: Some bacteria develop resistance through mutations that make target proteins less vulnerable; this is seen in the case of fluoroquinolones, where the target enzyme, DNA topoisomerases, has undergone a mutation [23]. For resistance to develop, the mutant must become dominant; simply incorporating the genes that code for the resistant enzyme is insufficient. In certain instances, plasmids can trigger the production of target enzymes, and they can also transmit resistance genes [24].

Preventing targets from obtaining drugs: It may be possible to reduce drug availability to targets topically or by triggering the efflux process. Reducing the inward migration across the outer membrane is how gram negative bacteria are handled.

Triclosan resistance mechanisms include:

Increased target expression combined with target mutation: A strain of *E. coli* developed cross-resistance to several antimicrobial drugs as a result of mutations at *fab-1* brought on by TCS treatment. This sparked the idea that antibiotics and biocides may share targets, and that their careless usage could lead to resistance to crucial medications. This conclusion has been supported by research showing that some mutations affecting *inhA* in *Mycobacterium smegmatis* and *Mycobacterium TB* resulted in resistance to TCS and to the medication isoniazid, which is used to treat tuberculosis resistance. Both *M. smegmatis* and *E. coli* mutants were discovered at the NADH binding site. Upregulation of transcription or translation was caused by a point mutation on *mabA* upstream near the ribosome binding site in *M. tuberculosis*. This mutation was also found in isolates that were resistant to isoniazid.

Detoxification mediated by the efflux pump: Active efflux in bacterial cells is another, potentially more pervasive, mechanism for TCS resistance. Bacteria are the primary classification for the five families of efflux pumps. All of these transporters work in tandem with some energy in the form of proton motive force to catalyze drug efflux pumps.

Table 3: Showing diverse families of Efflux pumps. (Source: Schweizer, H. P., 2001)

S.no.	Efflux pump family	Short name
1.	Resistance Nodulation Cell Division family	RND
2.	Major Facilitator Super family	MFS
3.	Small Multidrug Resistance family	SMR
4.	ATP binding Casette	ABC
5.	Multidrug and Toxic compound Extrusion family	MATE

The most complicated structures are seen in RND efflux systems, which catalyze drug efflux for two membranes. Up to 12 RND-type efflux operons, which are present in *Pseudomonas aeruginosa*, are encoded by chromosomes in different numbers [65]. In *Pseudomonas aeruginosa*, acquired resistance is primarily caused by low outer-membrane permeability, high lipid content, and active efflux. Following antibiotic treatment, some *P. aeruginosa* mutants have increased MexAB-OprM efflux operons and others that are only expressed [13, 30, 35, 52, 53]. Quorum-sensing regulates the transcription of several efflux pumps that are positively controlled [73]. However, the TCS resistance in *E. coli* is caused by the AcrAB-ToIC efflux pump. Experimental research revealed that TCS-resistant types with high OprJ, a component of the MexCD-OprJ system, were Triclosan-susceptible, while MexAB-OprM mutants with this system removed were found to be Triclosan-susceptible. According to these findings, TCS exposure to susceptible strains favors the development of multidrug-resistant strains linked to clinically significant resistance to other antibiotics [43].

Table 4: Showing examples of Efflux pump and their belonging family with their respective microorganisms. (Source: Schweizer, H. P., 2001)

S.no.	Example	Class	Microorganisms
1.	NorA	MFS	<i>Staphylococcus aureus</i>
2.	MexAB-OprM	RND	<i>Pseudomonas aeruginosa</i>
3.	LmrA	ABC	<i>Lactobacillus lactis</i>

Triclosan's enzymatic breakdown: Due to their continued growth on TCS-containing medium, the TriRY strain of *Pseudomonas putida* and the TR1 strain of *Alcaligenes xylosoxidans* were reported to have increased levels of resistance against TCS [44]. According to certain research, the identified TCS-resistant bacteria may be able to break down triclosan [69]. By prelabelling the TCS, *Sphingomonas* strain RD1 was likewise revealed to be concerned with TCS breakdown, as evidenced by the development of ¹⁴CO₂. It has been discovered that susceptible strains are incapable of mineralizing TCS [29]. Therefore, it is determined that TCS degradation is another likely mechanism of TCS resistance. Regarding the hydroxyl group, glucosylation and xylosylation were also seen for the mineralization of TCS in two root fungi, which may demonstrate resemblance to bacterial processes [26].

Triclosan and antibiotic cross-resistance

It was shown by new citations that TCS and antibiotics are related. Two primary findings provide a suitable illustration of this. First, there is a mechanism of resistance shared by TCS and antibiotics, which involves efflux pumps and regulatory alterations. Many clinical isolates that have been treated to different antibiotic concentrations are thought to express a large number of efflux pumps [28,54]. TCS and isoniazid resistance in a clinical isolate of *M. tuberculosis* were caused by a second upregulated mutation pathway. Target mutations, enhanced target expression, and enzymatic modification possibly the most important efflux pumps are all common resistance mechanisms shared by triclosan and antibiotics. As a result, their exploitative use might undoubtedly screen resistant organisms. Given the association between TCS and antibiotics, it is quite likely that TCS will develop antibiotic resistance. Therefore, there is a legitimate worry about raising public knowledge in order to stop the abusive use of TCS.

TCS exposure's impact on the gut microbiota

According to earlier research, being susceptible to TCS may result in a number of negative consequences, such as endocrine disruption, liver carcinogenesis, liver fibrosis, and antibiotic resistance. According to recent research, low-dose TCS exposure increases colon inflammation and exacerbates colon

carcinogenesis, which was linked to colitis in mice models, raising the possibility that TCS may negatively impact gut health. In mice lacking a gut microbiome or mice lacking the Toll-like receptor (TLR4-1, mice), a crucial regulator of host-microbe relations, TCS exposure alters gut microbiota and stops causing colonic inflammation. This suggests that gut microbiota supports the pre-inflammatory effects of TCS. All of our research indicated that TCS is of vital significance for gut health implications, given its widespread use in daily life. After receiving TCS for two to three weeks, C57BL/6 mice exhibit a reduction in diversity and a change in the composition of their gut microbiome, indicating that TCS has the capacity to disturb the gut microbiome. This conclusion was significantly impacted by earlier research that shown TCS exposure disrupts gut microbiota in a range of animal species, including rats, mice, zebra-fish, fathead minnows, and mice [46, 18, 25]. Prior research clearly showed that TCS has a high risk of disrupting the gut microbiota.

Enzymes and proteins of Bacterial Type II Fatty Acid Synthesis:

Table 5: Showing some enzymes and proteins of Bacterial Type II Fatty Acid Synthesis in tabulated form. (Source: Campbell, J. W., et. al. 2001.)

S. no.	Enzymes and proteins	Encoding genes
1.	Acetyl- Co A Carboxylase	fab H
2.	Malonyl- Co A: ACP Transacylase	fab D
3.	3- Ketoacyl- ACP Synthases I	fab B
	3- Ketoacyl- ACP Synthases II	fab F
	3- Ketoacyl- ACP Synthases III	fab F, fab H
4.	3- Ketoacyl- ACP Reductase	fab G
5.	3- Hydroxyacyl- ACP Dehydroase	fab Z, fab A
6.	Enoyl - ACP Reductase	Fab I

Drug-TCS antagonistic interaction

The antagonistic interaction of TCS with different medications can be explained by a number of ways. when fatal dosages of various medications, including vancomycin, ciprofloxacin, and rifampicin, were administered with TCS. *Staphylococcus aureus* may become more resilient and produce more biofilms [71]. Guanosine tetraphosphate (ppGpp) builds accumulated when TCS blocks fatty acids, suppressing the TCA cycle, decreasing metabolism, and increasing the rate at which biofilms are formed. Triclosan-induced oxidative stress-induced mutations in *E. coli* at genes such as *frdD*, *fab-1*, *acrR*, *marR*, and *soxR*, as well as overexpression of transcriptional genes coding for efflux pumps and enzyme β -lactamases, are linked to additional pathways [6,31,36]. The SOS response genes *dinD* and *umuC* in *E. coli* are activated by oxidative stress, which promotes the horizontal transfer of multi-resistance genes to *Pseudomonas putida* and other species [38]. By creating the bacterial membrane, it also prepares the transformation for extracellular genes. Tetracycline, carbapenem, and norfloxacin can all have antagonistic effects in *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, respectively, according to Shrestha et al. Findings regarding these proposed TCS may hasten the regulation of the efflux pump, causing the strains to become totally resistant to specific antibiotics [62].

Antibiotics and drugs working in concert

It has been discovered that a conjugate compound of TCS and ethylene polyglycol kills resistant strains of *E. coli*, *S. aureus*, and Streptococcal biofilm in the oral cavity more effectively than TCS taken alone [34]. Patients experience breathing difficulties as a result of mucus buildup in the respiratory alveolar region, which harbors the bacteria *P. aeruginosa* and increases infections in people with cystic fibrosis, a genetic condition. When used with tobramycin, TCS exhibits a synergistic effect that reduces the number of *Pseudomonas* inside the biofilm by a factor of 100 in the treatment of cystic fibrosis. In contrast to other sanitizers, it also demonstrates a decrease in the formation of *Listeria* biofilms. TCS disrupts the fatty acid biosynthesis pathway, which turns resistant strains of *Vibrio alginolyticus* into sensitive or Ceftazidime strains. For *Staphylococcus epidermidis*, TCS also shown a critical synergistic impact against erythromycin, ampicillin, and kanamycin [35].

Medical and commercial applications

Alfhili et al. have reported the molecular and biochemical nature of TCS, which was loaded with polyurethane micelles to treat certain bacterial infections and reduce biofilms by drug delivery. TCS is also used by the textile industry for their fabrics [27, 40]. TCS is also used to treat cancer, although it has been shown to be harmful to erythrocytes, perhaps causing hemolysis and early mortality through the stimulation of the MAP kinase pathway and calcium mobilization [60].

Catheters: Studies have explored coating catheters with TCS, a tiny antibacterial chemical, because urinary tract infections linked to catheters are common nosocomial infections in hospitals. *Proteus mirabilis* produces biofilms inside catheters that block flow, whereas TCS-impregnated catheter material completely inhibits crystalline biofilm [57] and *E. coli* colonization is likewise inhibited [66, 7].

Sutures: The third most common nosocomial infection is surgical site infection, which accounts for up to 16% of all infections and is dependent on the suture material. TCS-coated sutures aid in the prevention of surgical site infections, which affect a large number of patients undergoing hip, knee, colorectal, and tibial plateau procedures [71].

Dental implants: Compared to toothpaste without TCS, toothpaste containing TCS is more effective at maintaining the health of dental implants. Triclosan contained in Dentrifice can prevent enamel erosion, toothpaste containing fluoride and TCS can reduce inflammation of peri-implant mucositis, and TCS has been proposed as an effective periodontal therapy. The conjugate of triclosan and chitosan may offer stable, long-lasting sealing of the marginal implant and dentin contact [21, 41].

Adverse effects

TCS may enter our bodies through a variety of pathways. TCS is readily absorbed through the skin, bloodstreams [45] and other bodily organs through food and drink [58]. TCS may pass the blood-brain barrier and be broken down by certain xenobiotic enzymes [58,68]. Additionally, it may distort Ca²⁺ homeostasis and depolarize the plasma membrane close to the neuromuscular junction. TCS has the ability to cause oxidative stress, which can alter the way the cell cycle and apoptosis are regulated and cause endocrine disruption [8,33,51,80]. TCS exposure can cause osteoporosis in postmenopausal women and disrupt the sodium/iodide symporter [75] computational analysis, considering the idea that TCS's fine targets include protein kinase, B-cell lymphoma, and the signaling pathway of apoptosis. Exposure to TCS may alter gut microbiota, resulting in colon tumors and inflammation [59, 60, 77].

Conclusion

Triclosan can have both beneficial and detrimental effects on people. Its interactions as a biocide are contingent on the biocide's composition, the kind of organism or sample, and additional environmental variables. Antibiotics and TCS can react antagonistically as well as synergistically. According to this study and other research, the commonly used biocides and TCS may have a negative impact on gut microbiota. When TCS is drained into sewage, it seeps into the environment and may be harmful to both the environment and public health. It is important to carefully examine the health effects of long-term exposure to TCS because of its bioaccumulative tendency in various trophic levels of the ecosystem.

Future prospectives

Future research should focus on understanding the molecular mechanisms by which triclosan disrupts gut microflora and promotes antibiotic cross-resistance. Multi-omics approaches can reveal key resistance genes and pathways, while long-term animal and human studies can assess chronic effects. Investigating horizontal gene transfer via mobile genetic elements under triclosan pressure is crucial. Exploring microbiota-host interactions and environmental exposures will offer broader health insights. Development of microbiome-targeted interventions and integration of triclosan-linked resistance into global surveillance can inform public health policies and regulatory decisions, ultimately aiding in controlling the spread of antimicrobial resistance linked to common environmental biocides. Even though research has been done, more work is needed to fully understand how TCS affects gut health in humans.

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