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Adverse effects of triclosan exposure on health and potential molecular mechanisms

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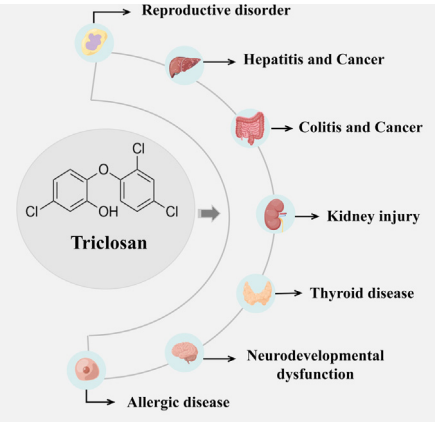
HIGHLIGHTS

- The use of triclosan has dramatically increased around the world because of COVID-19.
- TCS is frequently detected in the environment and human biological samples.
- TCS is a potential endocrine disruptor and has diverse adverse effects on health.
- For various harmful health effects, the safety of TCS deserves further discussion.

GRAPHICAL ABSTRACT



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ABSTRACT

With the COVID-19 pandemic, the use of disinfectants has grown significantly around the world. Triclosan (TCS), namely 5-chloro-2-(2,4-dichlorophenoxy) phenol or 2,4,4′-trichloro-2′-hydroxydiphenyl ether, is a broad-spectrum, lipophilic, antibacterial agent that is extensively used in multifarious consumer products. Due to the widespread use and bioaccumulation, TCS is frequently detected in the environment and human biological samples. Accumulating evidence suggests that TCS is considered as a novel endocrine disruptor and may have potential unfavorable effects on human health, but studies on the toxic effect mediated by TCS exposure as well as its underlying mechanisms of action are relatively sparse. Therefore, in this review, we attempted to summarize the potential detrimental effects of TCS exposure on human reproductive health, liver function, intestinal homeostasis, kidney function, thyroid endocrine, and other tissue health, and further explore its mechanisms of action, thereby contributing to the better understanding of TCS characteristics and safety. Moreover, our work suggested the need to further investigate the biological effects of TCS exposure at the metabolic level in vivo.

Contents

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1. Introduction

With the outbreak and epidemic of COVID-19, the use of disinfectants is expected to increase dramatically all over the world. Triclosan (TCS; 5-chloro-2-[2,4-dichloro-phenoxy] phenol) is a broad-spectrum, lipophilic, antibacterial agent. As a polychlorinated bisphenol compound, TCS has a distinct aromatic odor, not only easily soluble in water, but also well soluble in organic solvents, such as methanol, ethanol, and dimethyl sulfoxide (Alfhili and Lee, 2019). TCS has been extensively used in a variety of consumer products (Weatherly and Gosse, 2017), such as toothpastes, hand soaps, shampoos, cosmetics, and other consumer products, as well as in clinical settings (antiseptics, disinfectants) and medical devices (Montagnini et al., 2021). Currently, the detection rate of TCS in the environment is quite high and almost ubiquitous. TCS is a widespread environmental contaminant and has been determined in urine, blood, breast milk, amniotic fluid, and so on from the general population in different parts of the world (Etzel et al., 2017; Nasab et al., 2022; Weber et al., 2022). It is known that humans could be exposed to TCS through dermal contact and direct ingestion (Chen et al., 2019; Yueh and Tukey, 2016), whereas in the environment, TCS exposure occurs dominantly via the contaminated water, food, or animals (Milanović et al., 2021) (Fig. 1). Also, TCS has been detected to bioaccumulate in aquatic biota, such as algae (Mo et al., 2022), fish (Ku et al., 2014; Phillips et al., 2022), and marine mammals (Carey et al., 2016). Increasing literature has indicated that as a widely-used phenolic chemical, TCS has not only the endocrine-disrupting feature, but also the carcinogenic characteristic (Ashrap et al., 2017; Carey et al., 2016; Liu et al., 2022a; Yueh et al., 2014). In the research by Maksymowicz et al. (2022), TCS stimulated excessive proliferation of human ovarian cells by regulating the expression of genes involved in cell proliferation. Also, TCS was thought to potentially promote cancer metastasis through the epithelial-mesenchymal transition (EMT) process, in which cells lost their cell polarity, adhesion capacity, and thus initiated cancer progression and metastasis (Derouiche et al., 2017). In addition, mounting work has suggested that TCS exposure could contribute to other detrimental health effects, such as hepatic and renal toxicity (Ena et al., 2018; Tang et al., 2018), intestinal damage (Zhang et al., 2022a), thyroid function impairment (Milanović et al., 2021). However, the mechanisms by which TCS mediated negative health effects are still obscure (Gore et al., 2015).

At present, the reviews on TCS predominantly discuss epidemiological studies and environmental effects. Therefore, this paper reviews the literature on TCS exposure in humans and animals and cells, and further summarizes the deleterious effects and potential mechanisms of action of TCS accumulation in various tissues. A deeper and more comprehensive understanding of TCS safety has been gained from these insights.

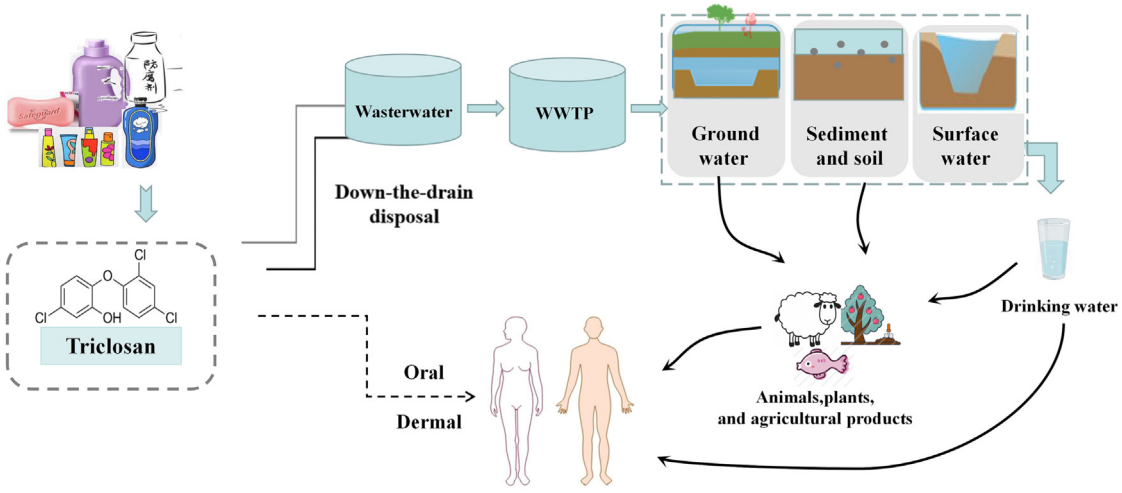

Fig. 1. A schematic model demonstrated the potential exposure routes of triclosan (TCS). TCS could be exposed to humans not only through the dermal contact and direct ingestion, but also via the contaminated water, food, plants, or animals.

2. Methodology

Literature search databases included PubMed, EMBASE, and Google Scholar up to January 2023. To find out relevant literature, search terms were consisted of “triclosan”, “human health effects”, “reproductive disorders”, “liver toxicity”, “intestinal homeostasis”, and “renal function”. From these searches, studies evaluating effects of TCS on health were screened out and identified. A total of 117 studies were met the inclusion criteria: (a) papers published since 2010, (b) available as full-text publications, (c) studies conducted on animals or humans, and (d) original or review articles.

3. Triclosan-induced toxic effects

3.1. Reproductive toxicity of triclosan

Growing research has suggested that the impairment of reproductive health is associated with environmental exposure to many chemicals, such as EDCs (Hipwell et al., 2019; Mínguez-Alarcón et al., 2019; Xu et al., 2022), which could influence reproductive health by regulating receptor binding, hormone biosynthesis, transport, metabolism, non-EATS pathways (Delbes et al., 2022), and so on. TCS is an emerging endocrine disruptor that could give rise to reproductive disorders in both men and women (Raj et al., 2021).

3.1.1. Effects of triclosan on male reproductive health

In mature male Wistar rats, a decline in the number of actively moving sperm and a reduction in testicular weight were observed after treatment with TCS (Yuan et al., 2022). Lan et al. (2015) assessed whether TCS exposure had adverse effects on sperm or reproductive organs in mammals, finding that TCS displayed a trend to accumulate in the epididymis of male Sprague Dawley (SD) rats and that rats treated with high doses (200 mg/kg) of TCS showed a significant decrease in daily sperm production (DSP), changes in sperm morphology, and an increase in the number of malformed sperm. Similar findings were reported in recent epidemiological studies, which pointed out that TCS exposure might negatively influence the semen quality (Jurewicz et al., 2018; Zhu et al., 2022). Exposure to low-level TCS brought about adverse effects on male semen quality, with an increases in sperm LIN and WOB observed in the third quartile of TCS exposure, implying a potential non-linear effect on male reproduction (Yuan et al., 2022). Moreover, low-level TCS exposure damaged sperm DNA and increased the percentage of sperm morphological abnormalities (Jurewicz et al., 2018). In a recent box of prospective studies, TCS exposure concentrations were divided into three tiers by determining urine samples from men, and the highest TCS exposure level was significantly associated with increased infertility, results demonstrating that the TCS exposure concentration was correlated positively with infertility, whereas negatively with fertility (Zhu et al., 2022). Furthermore, TCS also had the potential to influence hormone receptor expressions directly and indirectly or restrain testicular steroidogenesis, thereby perturbing male reproduction and fertility (Ha et al., 2018; Wang et al., 2018a; Yu et al., 2021). As expected, the deleterious effect of TCS on reproduction also frequently appeared in diverse animal models. A study on adult zebrafish revealed that TCS could disturb testicular development and spermatogenesis by interfering with sex hormone levels (Qiao et al., 2022). Likewise, our previous work uncovered the abnormal alteration in testicular tissue morphology and the suppression of testosterone biosynthesis in Leydig cells after TCS exposure (Duan et al., 2020). In addition, it is shown that TCS exposure may exert carcinogenic effects on reproductive organs (Derouiche et al., 2017; Lee et al., 2017). TCS stimulated human prostate cancer stromal cells to secrete vascular endothelial growth factor (VEGF), a factor that promotes tumor growth (Derouiche et al., 2017), and it could also advance prostate cancer metastasis through regulating epithelial mesenchymal transition (EMT) markers as well as related signaling pathways (Lee et al., 2017). From these studies, we have summarized the potential effects of TCS exposure on the male reproductive system (Table 1).

Table 1
Summary of male reproductive toxicity of triclosan.

TCS exposure negative effects	Males
Semen quality	TCS exposure increased the percentage of morphologically abnormal sperm (Lan et al., 2015) and decreased the number of actively moving sperm (Delbes et al., 2022). Rats treated with high doses (200 mg/kg) of TCS showed a significant decrease in daily sperm production (DSP), changes in sperm morphology, and an increase in the number of malformed sperm (Lan et al., 2015)
Steroidogenesis	Inhibition of testosterone biosynthesis by suppressing steroidogenic enzyme activity through the regulation of various microRNA pathways (Ha et al., 2018).
Reproductive hormone levels	Long-term exposure to TCS interfered with sex hormone levels to impair reproduction of zebrafish. Testosterone levels were reduced, while E2 and Vtg were significantly elevated in zebrafish. TCS perturbed the testicular development and spermatogenesis (Duan et al., 2020).
Carcinogenic effect on reproductive organs	Studies have shown that TCS induced cell division in various tissues including the reproductive system, and TCS also promoted cancer progression by activating membrane ion channels (Maksymowicz et al., 2022). Moreover, TCS stimulated VEGF secretion through TRPAI channels and proliferated human prostate cancer cells to exert oncogenic effects (Lee et al., 2017).

3.1.2. Effects of triclosan on female reproductive health and offspring

There is evidence that TCS exposure may interfere with ovarian functions as well as ovarian reserve (Jurewicz et al., 2019; Kim et al., 2014; Maksymowicz et al., 2022). The research performed in zebrafish revealed that high-dose TCS exposure resulted in ovarian oxidative damage and then accelerated ovarian cell apoptosis (Wang et al., 2020a). According to the work by Du et al. (2021), TCS exposure disordered energy metabolism by dominating glucose flow to perturb steroid hormone biosynthesis and hormone homeostasis, and then affected female reproductive development. In adult female mice, TCS exposure downregulated thyroid hormone levels, led to hyperprolactinemia, and then restrain hypothalamic kisspeptin expression, finally giving rise to reproductive endocrine disturbance and functional defects (Cao et al., 2018).

Furthermore, due to the increasing use of various daily products containing TCS, several epidemiological studies have pointed out a possible association between TCS and infertility and neonatal birth defects (Feng et al., 2016; Guo et al., 2021; Priyanka et al., 2020). Patti et al. (2021) assessed the relationship between TCS exposure during pregnancy and infant birth weight via the systematic evaluation and meta-analysis, and a significant negative association between TCS concentration and infant birth weight was observed in those with higher TCS exposure. Wang et al. (2018b) investigated the potential effects of antenatal TCS exposure on fetal reproductive hormones in cord blood and the underlying mechanisms related to placental steroidogenic enzymes, confirming that antenatal TCS exposure was associated with the testosterone concentration in cord blood in a dose-dependent manner and male infants were more sensitive and vulnerable to TCS exposure. Likewise, a significant association between prenatal and early TCS exposure and allergic diseases was manifested in children (Lee-Sarwar et al., 2018). In the medaka model, TCS-exposed embryos developed malformations in the early life stage and TCS in this range might alter the sex ratio of developing embryos (Song et al., 2020) (Table 2).

In conclusion, these studies have favorably demonstrated that TCS has the reproductive interference effect. In males, TCS may reduce testosterone levels by interacting with hormone receptors or by disrupting testicular steroid production. In addition, the bioaccumulation of TCS in reproductive organs may directly affect sperm synthesis and semen quality and have carcinogenic effects on reproductive organs. And in females, TCS exposure not only influences reproductive hormone levels, but also leads to the impairment of ovarian function and even has an impact on the next generation.

Table 2
Summary of effects of triclosan on female reproductive health and offspring.

TCS exposure negative effects	Females and offspring
Ovarian function	Higher doses of TCS led to ovarian oxidative damage and advanced reactive oxygen-dependent ovarian apoptosis (Guo et al., 2021). Urinary TCS concentration was also negatively correlated with sinus follicle count, negatively impacting ovarian reserve (Wang et al., 2020b).
Steroidogenesis	TCS could disorder energy metabolism and disrupt hormone homeostasis by dominating glucose flow to steroid hormone biosynthesis (Huang et al., 2020).
Reproductive hormone levels	Adult female mice exposed to TCS showed the lower serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone, and gonadotropin releasing hormone (GnRH) mRNA levels (Cao et al., 2018).
Carcinogenic effect on reproductive organs	TCS facilitated ovarian cancer growth by regulating cell cycles and apoptosis-related genes through an ER-dependent pathway (Du et al., 2021).
Impact on offspring	Exposure to TCS during pregnancy and lactation could adversely influence the reproductive function and fertility in male rats of the F1 and F2 generations (Feng et al., 2016; Wang et al., 2018c), and lead to the decline of uterine weight and the occurrence of miscarriages (Patti et al., 2021). In addition, there was a significant association between prenatal TCS exposure and allergic disease in children (Lee et al., 2017).

3.2. Gastrointestinal toxicity of triclosan

3.2.1. Hepatotoxicity of triclosan

Mounting evidence has indicated that the liver is a predominant organ of TCS metabolism and detoxification. Huang et al. (2020) employed GC-ECNI/MS to determine TCS levels in different human tissues and affirmed that the liver was the organ with the highest TCS concentration. Hepatotoxicity studies of TCS in different species have suggested that TCS exposure has harmful effects on the liver and may lead to the development of non-alcoholic fatty liver disease (NAFLD) (Li et al., 2023), hepatitis (Zhang et al., 2022b), and even liver cancer (Zhang et al., 2019). In mice, it was reported that TCS exposure triggered the disturbance of hepatic lipid metabolism and then promoted hepatic impairment (Zhang et al., 2022a). After 21 days of TCS exposure via lactation, the delivery of TCS contributed to the premature development of fatty liver in neonatal mice, which exhibited early onset liver endoplasmic reticulum (ER) stress and steatosis (Weber et al., 2022). In SD rats, perinatal TCS exposure gave rise to metabolic and gut microbiota disturbance in the offspring (Ma et al., 2020). Meanwhile, Yueh et al. (2020) explored the relationship between TCS and NAFLD and discovered that TCS could exacerbate the high-fat diet-induced metabolic disorder by impairing the regulation of fibroblast growth factor 21 (FGF21) expression. In addition, the prevalence of TCS in aquatic environments has made animal models of this habitat the subject of extensive studies of TCS toxicity. In peacock fish, TCS had the highest concentration in the liver (Escarrone et al., 2016). In a zebrafish model, TCS exposure resulted in the accumulation of lipid droplets in the liver by interfering with hepatic lipid metabolism (Wang et al., 2020b). Another study also revealed that the toxicity of TCS was closely associated with the induction of apoptosis in hepatocytes (Liu et al., 2019). Sun et al. (2021a) unveiled that chronic exposure to TCS in zebrafish triggered fatty liver and hepatitis, which were related to the expression of miR-30b and its targeted gene fat mass and obesity-associated protein (FTO). Likewise, Bao et al. (2021) estimated the toxic effects of TCS on mosquito fish and revealed that exposure to environmentally relevant concentrations of TCS could activate the nuclear factor E2-related factor 2 (Nrf2) protein expression in the liver of mosquito fish and cause oxidative stress to the exposed organisms. In an in vitro study, however, Sun et al. (2021b) showed that TCS suppressed fatty acid synthesis and human HepG2 cell growth by downregulating fatty acid synthase through multifarious miRNAs. Interestingly, another study uncovered that TCS weakened overall DNA methylation levels in HepG2 cells and accelerated hepatocarcinogenesis and progression (Ma et al., 2013). Thus, based on these ex vivo and in vivo studies, it is concluded that TCS exposure primarily contributes to disturbance in hepatic lipid metabolism, leading to the premature development of fatty liver, such as a study reporting that neonatal mice could increase the susceptibility to non-alcoholic fatty liver disease (NAFLD) through lactational exposure to TCS. However, there is a serious lack of studies in this direction that have been conducted on humans or human-derived tissues. This also informs us of the greater need for future longitudinal epidemiological studies to examine the correlation between TCS exposure concentrations and liver disease. The hepatotoxicity of TCS exposure has been summarized in Table 3.

3.2.2. Intestinal toxicity of triclosan

Triclosan is frequently used as an antibacterial agent in a variety of consumer products such as toothpaste and soap. Surprisingly, one study reported that TCS-containing soaps failed to provide any additional skin disinfection benefits in comparison to TCS-free soaps (Kim et al., 2015). Several recent studies displayed that low-dose TCS exposure could not only aggravate colonic inflammation and exacerbate colitis-related colon tumorigenesis (Liu et al., 2022a; Sanidad et al., 2019; Yang et al., 2019), but also interfere with the gut microbiota in mouse models (Hu et al., 2016; Yang et al., 2018), indicating that TCS might detrimentally affect gut health. Gaulke et al. (2016) exposed adult zebrafish to food containing TCS for four to seven days and then analyzed their microbial communities using 16S rRNA amplicon sequencing, data exhibiting that TCS exposure disturbed the composition and ecological dynamics of microbial communities in the gut of zebrafish and then facilitated the instability and reorganization of microbial communities. The findings were in line with that of the study by Zang et al. (2019), which observed that TCS exposure perturbed the intestinal mucosal immune system and intestinal microflora of adult zebrafish. In other fish, low-level TCS exposure also interfered with

Table 3
Summary of liver toxicity of triclosan.

Models	Hepatotoxic effects	References
C57BL/6 mice	TCS-exposed mice showed hepatic hypertrophy, increase in liver lipid levels, and upregulation of fatty acid oxidation and inflammation-related genes.	Huang et al., 2020
C57BL/6 mice	TCS aggravated high-fat diet-induced metabolic disorders by disrupting the regulation of FGF21 expression.	Yueh et al., 2020
Sprague Dawley (SD) rats	More upregulated genes in carbohydrate and lipid metabolic pathways were observed in aged rats as TCS exposure contributed to metabolic disturbance and these effects would accumulate over time.	Ma et al., 2020
C57/B6 mice	TCS transmission through lactation resulted in adipogenesis, ER stress, PPARα activation, immune inflammation in the neonatal liver, and nonalcoholic fatty liver disease in neonatal C57/B6 mice.	Weber et al., 2022
Zebrafish	TCS regulated fto-mediated m6 methylation by inhibiting miR-30b expression, which led to the disturbance of lipid metabolism and elevation of TG and TC levels in zebrafish.	Sun et al., 2021a
Zebrafish	Severe hepatocyte atrophy and necrosis in the liver tissue of zebrafish larvae after TCS exposure, with a marked increase in the gap between the liver plates.	Liu et al., 2019
Mosquito fish	TCS exposure perturbed the antioxidant system in mosquito fish liver tissues, and a number of oxidative stress-related biomarkers were displayed in a concentration-dependent (e.g. NQO1 mRNA, CAT mRNA) and/or time-dependent (e.g. GSH content) manner.	Bao et al., 2021
HepG2 cells	TCS treatment significantly restrained DNA methylation levels and suppressed DNA methyltransferase 1 activity in HepG2 cells.	Ma et al., 2013

microbial nitrogen metabolism in the fish gut (Narrowe et al., 2015). Furthermore, in mouse models, short-term exposure to TCS at relatively low doses brought about low-grade colonic inflammation in normal C57BL/6 mice, whereas in dextran sulfate sodium (DSS)-induced C57BL/6 mice, TCS treatment exacerbated colitis in mice as well as colonic tumourigenesis and shortened the colonic length (Sanidad et al., 2022; Yang et al., 2018). At the cellular level, Wang et al. (2018c) reported that TCS mediated autophagy in macrophages and non-phagocytic cells in vitro, killing *E. faecalis*, Lactobacillus and *E. coli*, disrupting the balance of the intestinal flora, and having a carcinogenic characteristic. In a previous epidemiological study, however, Adgent and Rogan (2015) examined the association between TCS and enterolactone, and the cross-sectional survey found that TCS exposure was not correlated with the production of enterolactone. Nevertheless, the use of enterolactone, an intestinal metabolite, as a marker of gut flora function is novel but crude, and only provides limited information about overall gut health. In summary, these studies have convincingly indicated that TCS exposure may exacerbate the development of colitis and colon tumors, alter the diversity of the intestinal microbiota, and lead to disorders of the intestinal flora. Therefore, the effects of TCS exposure on the human microbiota deserve further exploration. The intestinal toxicity of TCS exposure has been summarized in Table 4.

3.3. Nephrotoxicity of triclosan

The kidney is critical in the elimination of toxins, yet there is evidence that exposure to environmental pollutants may lead to early kidney injury, chronic kidney disease (CKD), and end-stage renal disease (ESRD) (Ena et al., 2018; Lim and Yoon, 2019; Zheng et al., 2017). A previous epidemiological investigation revealed that TCS exposure was positively associated with urinary β2-microglobulin expression which is a marker of early kidney injury (Lim and Yoon, 2019). In a rat model study, Ena et al. (2018) investigated the toxic effect of subchronic TCS exposure on male rat kidneys and demonstrated that high-dose TCS exposure induced histological changes as evidenced by the reduced Bowman's space, tubular lumen occlusion, and tubular epithelial cell degeneration. Moreover, Huang et al. (2023) discovered that TCS treatment gave rise to renal lipid accumulation and disruption of fatty acid metabolism in mice, finally leading to renal impairment of male C57BL/6 mice. In addition, several studies have proposed the pro-oxidant effect of TCS (Teplova et al., 2017), while oxidative stress could also lead to decreased renal function through inflammation, glomerular filtration barrier damage, and fibrosis (Ratliff et al., 2016). In human HRGEC cells, TCS treatment brought about oxidative stress and apoptosis, and then mediated kidney damage (Ma et al., 2022). Through these studies, it is concluded that TCS exposure dominantly disrupts the glomerular filtration barrier and causes impairment of renal function. However, systematic studies on the effect of TCS on the kidney are still largely lacking.

Table 4
Summary of intestinal toxicity of triclosan.

Models	Enterotoxic effects	References
C57BL/6 mice	TCS exacerbated colitis through a gut microbiota-dependent mechanism by which gut microbial GUS proteins mediated the colonic reactivation of TCS from its inactive glucosinolate metabolites and drove the intestinal toxicity of TCS in the process.	Zhang et al., 2022b
C57BL/6 mice	TCS exposure triggered low-grade colonic inflammation, increased colitis, and exacerbated colitis-associated colon cancer in mice, and it adversely influenced colonic inflammation and associated colon tumorigenesis primarily by modulating intestinal microbiota and TLR4 signaling.	Yang et al., 2018
Sprague Dawley (SD) rats	Low-dose TCS treatment disordered the intestinal microbiota in adolescent rats and led to an increase in the abundance of Spirochetes.	Hu et al., 2016
C57/B6 mice Balb/c mice	TCS exposure changed the diversity and composition of the intestinal microbiota in Balb/c mice. TCS treatment upregulated levels of sexual cytokines in the DSS-induced mouse model, decreased Occludin levels, and exacerbated the extent of intestinal mucosal and crypt damage, inflammatory cell infiltration, and glandular cell heterotype.	Liu et al., 2022c
Zebrafish	TCS exposure led to the disorder of zebrafish intestinal metabolism, as well as abnormalities in the intestinal mucosal immune system, while TCS treatment resulted in upregulation of pro-inflammatory genes (IL-1β, TNF-α) and elevated MDA concentrations.	Zang et al., 2019
Zebrafish	TCS exposure impaired the structure and ecodynamics of the adult zebrafish gastrointestinal microbiome.	Gaulke et al., 2016
Pimephales promelas	The *Pimephales promelas* gut microbiome was rapidly and significantly altered after exposure to low levels of environmentally relevant TCS, but recovered from this short-term perturbation in a fairly short period of time.	Narrowe et al., 2015
Raw264.7/ HeLa cells	TCS mediated autophagy of HeLa and Raw264.7 cells probably via the AMPK/ULK1 and JNK/ERK/p38 pathways in a dose-dependent fashion.	Wang et al., 2018c

3.4. The toxicity of triclosan on other organs

Apart from those harmful effects of TCS mentioned above, several literature has referred to other deleterious health effects mediated by TCS exposure in the past few years, such as the thyroid function damage (Zhang et al., 2018), neurodevelopmental toxicity (Wang et al., 2021), immune dysfunction (Bera et al., 2020; Zhao et al., 2022), and cytotoxicity (Querido et al., 2022). In cohort studies, TCS exposure was significantly correlated with the allergic disease in preschool children (Lin et al., 2022; Spanier et al., 2014), and the estrogenic effect of TCS might affect the prognosis of female breast cancer (Ilozumba et al., 2022). Moreover, it was reported that TCS exposure triggered neurotoxicity (Wang et al., 2022). Diao et al. (2022) recently elucidated that TCS exerted neurodevelopmental toxicity by upregulating miR-144 expression and causing abnormal regulation of neurologically related genes. Also, neurobehavioral toxicity was observed in the offspring of mice treated subcutaneously with TCS (Tran et al., 2020). Zhang et al. (2018) investigated the potential effect of TCS exposure on the thyroid function in SD rats and noted that TCS decreased thyroid hormone levels including total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), and free triiodothyronine (FT3) by restraining thyroid peroxidase (TPO). In a zebrafish model, Tang et al. (2022) discovered that exposure to TCS postponed the hatching of zebrafish embryos and downregulated TT4 and FT3 levels in zebrafish larvae and FT4 levels in adult zebrafish. Meanwhile, a recent epidemiological study pointed out a significant inverse association between maternal urinary TCS and cord blood FT3 as well as maternal blood FT4 and TSH concentrations in late pregnancy (Wang et al., 2017a). Furthermore, a latest research discovered that TCS induced immunotoxicity in zebrafish by regulating post-miR-19a and socs3b expressions, as well as the expression of II-6 and STAT3 (Zhao et al., 2022). Querido et al. (2022) revealed that self-sterilizing coatings containing TCS manifested low levels of cyto- and genotoxicity. Thus, these effects discussed in this section, together with relevant in vitro and in vivo studies, provide support for the epidemiological findings and suggest that the safety of TCS as a bacteriostatic agent remains highly controversial.

4. Potential mechanisms of triclosan-induced toxic effects

4.1. Triclosan and reproductive function disruption

Epidemiological studies have suggested that TCS exposure may influence semen quality (sperm alignment, viability, morphology, CASA parameters) and damage sperm DNA (Jurewicz et al., 2018). The biological mechanism by which TCS affects semen quality is currently uncertain.

However, in vitro studies in zebrafish demonstrated that TCS affected the testicular development and perturbed spermatogenesis by depressing the hormone biosynthesis of male zebrafish, such as testosterone (T), estradiol (E2), and vitellogenin (Vtg) (Qiao et al., 2022). Arginine is the main component of sperm proteins and has an essential role in promoting sperm production and providing energy for sperm motility (Ma et al., 2019). Exposure to TCS gave rise to a significant decrease in arginine synthesis and expression of retinoic acids (cyp3a65 and ugt1a1), ultimately leading to a reduction in sperm count (Qiao et al., 2022). Meanwhile, in female zebrafish, high concentrations of TCS were suspected to cause a significant decline in zebrafish spawning capacity and to downregulate Vtg levels in female zebrafish through estrogenic effects, thereby lowering mature oocyte and egg production (Qiao et al., 2022). The study performed in zebrafish reported that after exposure to TCS for 42 days, an accumulation in the malondialdehyde (MDA) content in the ovaries of the high-dose TCS group, an elevation in similar to metallothionein-B (sMT—B) and Bax gene expression, and a decline in Bcl-2/Bax ratio were observed, which eventually contributed to oxidative damage to the ovary, caused mitochondrial disorders, and accelerated ovarian apoptosis (Wang et al., 2020a). Moreover, Lin et al. (2017) evaluated the relationship between TCS-induced toxic processes and microRNA expression in a zebrafish model, concluding that TCS exposure led to the upregulation of mature miR-125b that was concomitant with consistent changes in pri-mir-125b-1 and pri-mir-125b-3 among its 3 pri-mir-125bs. It is known that steroidogenesis could be regulated by microRNAs through diverse pathways, such as modulating the expression of their target mRNAs and related molecules involved in spermatogenesis (Duan et al., 2020). Our previous research noted that TCS restrained testicular steroidogenesis through the miR-6321/JNK/Nur77 cascade response in male SD rats given TCS daily for 31 days by gavage (Ha et al., 2018). We also found that in male SD rats and Leydig cell lines, TCS induced miR-142-5p overexpression in testicular tissues of rats, then directly suppressed the Jak1/Stat1 pathway, and increased Dax1 expression, eventually leading to the inhibition of steroidogenic protein P450c17 and subsequent repression of testosterone biosynthesis (Duan et al., 2020). Additionally, other studies have indicated that TCS could interference with reproductive health through oxidative stress, lipid metabolism disorder, apoptosis, and other related signaling pathways (Kim et al., 2014; Zang et al., 2019). A gestational mouse model study, displayed that TCS influenced placental development through the peroxisome proliferator-activated receptor-γ (PPARγ) pathway and PPARγ activation or overexpression antagonized the TCS-induced increase in inflammatory gene expression (Li et al., 2021). Reports by Qiao et al. (2022) speculated that TCS might alter sex hormone levels by interfering with the lipid metabolism of ovarian cells, finally leading to reproductive dysfunction. In contrast, in in vitro studies, TCS stimulated ovarian cancer growth by regulating cell cycles and apoptosis-related genes through an ER-dependent pathway (Kim et al., 2014). Furthermore, Huo et al. (2022) reported that TCS modulated the miR-218-1-3p/SLC35C1 axis to regulate the proliferation, migration, invasion and inflammatory response of trophoblast cells in vitro, providing new insights into the prevention of spontaneous abortion.

Collectively, TCS could interfere with reproductive health through oxidative stress (Basini et al., 2022), hormonal dysregulation (Arismendi et al., 2022; Basini et al., 2021; Dong et al., 2022), germ cell autophagy and apoptosis (Liu et al., 2022b), steroidogenesis suppression (Yawer et al., 2020), and mitochondrial dysfunction (Du et al., 2021) (Table 5), although the specific mechanisms of action of TCS in infertility are still not fully elucidated yet. For example, does TCS exposure affect spermatogenesis by the disturbing blood-testis barrier, or affect semen quality by inducing apoptosis or pyroptosis of spermatogonia and spermatocytes? These are all areas for further research and discussion in the future.

4.2. Triclosan and hepatotoxicity

The liver plays a crucial role in metabolism. Accumulating studies have demonstrated that long-term exposure to TCS might have unfavorable health effects on the liver, and it could perturb liver metabolic function, aggravate liver fibrosis, accelerate hepatocellular carcinoma development through lipid metabolism disorder (Huang et al., 2020; Weber et al., 2022), induce oxidative stress (Wang et al., 2017b), facilitate mitochondrial dysfunction (Belosludtsev et al., 2018; Pereira-Maróstica et al., 2022; Tenkov et al., 2022), and modulate hepatocyte apoptosis (Liu et al., 2019). Free fatty acids (FFAs) are an important source of lipid synthesis and a recent research exhibited that both FFAs levels and fatty acid uptake related gene expressions were significantly elevated in mice exposed to TCS, including fatty acid translocase (Fat, also known as Cd36), fatty acid transport proteins 2 and 5 (Fatp2 and Fatp5) (Huang et al., 2020). The accumulation of hepatic triacylglycerols (TG) might be associated with increased effectiveness of FFAs and upregulation of TG biosynthesis-related genes, including phosphatidic acid phosphate hydrolase (Lpin1) and diacylglycerol o-acyltransferases 1 and 2 (Dgat1 and Dgat2). In contrast, hepatic TG accumulation was usually considered benign to hepatic steatosis (Paul et al., 2022). Here, it was also noted that TCS was able to activate peroxisome proliferator-activated receptor α (PPARα) without altering PPARα levels, whereas it induced the mRNA expression of PPARα-targeted genes, such as Cyp4a10 and Cpt1. As Cyp4a10 plays an important role in microsomal fatty acid (FA) β-oxidation, all these alterations gave rise to mitochondrial dysfunction and exacerbated liver impairment. The findings were supported by other study, which reported that TCS induced PPARα targets, cytochrome P450 4A (CYP4a) and acyl-coenzyme A oxidase 1 (ACOX1), and then contributed to the increase in liver weight and hepatocyte peroxisome production (Tang et al., 2018). In addition, increased FA oxidation and the risk of reactive oxygen species (ROS) production with increased acyl carnitine (AcCa) levels in the liver of TCS-exposed mice had been implicated (Huang et al., 2020). Several studies have indicated that TCS could induce oxidative stress to promote the hepatocellular carcinoma development and ROS production, acting as a liver tumor promoter (Yueh et al., 2014). Yueh et al. and Wang et al. administered TCS treatment in the diet and reported that TCS exposure resulted in upregulated expression of key antioxidant enzymes (HO-1, Gsta1) and oxidative stress-related genes such as Gpx1 and Aox1 in the liver of C57B/L mice. In a zebrafish model, Liu et al. (2019) displayed that TCS exposure accumulated MDA content and activated the MAPK/p53 signaling pathway to induce hepatic oxidative stress. TCS treatment brought about the accumulation of 8-OHdG in human HepG2 cells, sustaining the notion that TCS exposure contributed to oxidative DNA damage (Ma et al., 2013). In addition, a previous work manifested that increased inflammation was also considered to be the most common and relevant mechanism of liver damage (Todoric et al., 2020). In contrast, ceramide (Cer), a member of the sphingolipid family of lipids, is not only an essential component of the cell membrane but also has cell signaling properties (Han, 2016). Cer could also regulate the expression of pro-inflammatory genes via activating the nuclear factor kappa light chain enhancer (NF-κB) in activated B cells, and then promote a sustained and robust feedback mechanism (Pan et al., 2021). A study by Huang et al. (2020) demonstrated a significant increase in Cer levels in TCS-exposed mice and an increase in inflammatory cytokine (TNF-α, IL-1β and IL-6) mRNA expression was observed. In other in vivo studies, TCS stimulated ER stress in primary hepatocytes, activated transcription factor 4 (ATF4) through protein kinase R-like kinase (PERK) activation, finally contributing to the progression of simple steatosis to NASH (Weber et al., 2022).

In summary, in addition to the disorder of lipid metabolism, oxidative stress, inflammation, endoplasmic reticulum stress, and mitochondrial dysfunction discussed above (Fig. 2), TCS-mediated hepatotoxicity might be correlated with the disturbance of bile acid metabolism (Song et al., 2022) and immune dysfunction (Liu et al., 2019). However, the deleterious effects of TCS exposure on the liver in mammals in vivo have been explored rarely, especially underlying molecular mechanisms. Therefore, we could combine metabolomics and lipidomics to reveal the metabolic mechanism of TCS-induced hepatocyte toxicity in the future. In addition, the role of gut microbiota on TCS-induced liver injury is still unknown, which should also be the focus of our future research.

Table 5
Summary of potential mechanisms of TCS-induced reproductive disorders.

References	Models	Mechanisms	Target genes/proteins/biomarkers	Responses
Qiao et al., 2022	Zebrafish(male)	Hormone synthesis	E2	Upregulated by TCS
			VTG	Upregulated by TCS
Arismendi et al., 2022	Sprague Dawley rats	Hormonal imbalance	P4	Downregulated by TCS
			T	Downregulated by TCS
Li et al., 2021	HTR-8/SVneo cells JEG-3 cells	PPARγ pathway	PPARγ	Downregulated by TCS
		Inflammation	IL-6	Upregulated by TCS
			TNF-α	Upregulated by TCS
			IL-1β	Upregulated by TCS
		Cell migration	P65	Upregulated by TCS
			MMP-2	Downregulated by TCS
			MMP-9	Downregulated by TCS
Liu et al., 2022c	Zebrafish	Oxidative stress	ROS	Upregulated by TCS
			SOD	Upregulated by TCS
			P53	Upregulated by TCS
		Apoptosis	Caspase-8	Upregulated by TCS
			Caspase-3	Upregulated by TCS
			Caspase-9	Upregulated by TCS
			Cldn7	Upregulated by TCS
			Crb3	Upregulated by TCS
Dong et al., 2022	ICR mice	Receptivity of uterus	ERα	Downregulated by TCS
			c-Jun	Upregulated by TCS
Huo et al., 2022	JEG3 cells HTR-8 cells	Cell proliferation, migration, invasion	miR-218-1-3p	Upregulated by TCS
			SLC35C1	Downregulated by TCS
Du et al., 2021	KGN cells Primary rGCs cells	Steroidogenesis	P4	Upregulated by TCS
			HSD3B2	Upregulated by TCS
			E2	Upregulated by TCS
			HSD17B1	Upregulated by TCS
		Mitochondrial damage	ATP	Downregulated by TCS
			PKM2	Upregulated by TCS
			GLUT1	Upregulated by TCS
			miR-142-5p	Upregulated by TCS
Duan et al., 2020	Sprague Dawley rats	Testosterone synthesis	P450c17	Downregulated by TCS
			Sp1	Downregulated by TCS
			DAX1	Upregulated by TCS
			Cx43	Downregulated by TCS
Yawer et al., 2020	TM3 Leydig cells	Testicular cell signaling	p-Erk1/2	Upregulated by TCS
			p38/MAPK	Upregulated by TCS
Wang et al., 2020a	Zebrafish	Oxidative stress	SOD	Downregulated by TCS
			CAT	Downregulated by TCS
			SMT-B	Downregulated by TCS
		Apoptosis	MT-2	Upregulated by TCS
			Bax	Upregulated by TCS
			Bcl-2	Downregulated by TCS
			miR-6321	Upregulated by TCS
Ha et al., 2018	Sprague Dawley rats	Steroidogenesis	P-JNK	Downregulated by TCS
			P-c-Jun	Downregulated by TCS
			Nur77	Downregulated by TCS
Basini et al., 2022	Swine Granulosa Cells	Steroidogenesis	E2	
			P4	Downregulated by TCS Downregulated by TCS
		Oxidative stress	NO	Downregulated by TCS Upregulated by TCS
			SOD	Downregulated by TCS
			O_2^-	
Basini et al., 2021	Swine Luteal Cells	Hormonal imbalance Oxidative stress	ATP	Downregulated by TCS
			P4	Downregulated by TCS
			NO	Upregulated by TCS
			SOD	Downregulated by TCS

4.3. Triclosan and intestinal injury

Previous studies displayed that TCS exposure facilitated colonic inflammation and aggravated the severity of colitis and colon cancer (Yang et al., 2018), but detailed mechanisms by which TCS led to colonic inflammation and associated colon tumourigenesis are currently unknown. A latest cohort study detected the unconjugated OH-TCS metabolite in human feces of TCS-exposed subjects. Aromatic hydroxylation is the predominant oxidative metabolic process of TCS and is associated with its toxicological effects in host tissues (Zhang et al., 2023). In a study by Yang et al. (2019), TCS was exposed to C57BL/6 mice via diet for three weeks and the results showed that TCS triggered colonic inflammation in mice by disturbing the intestinal microbiota and activating the Toll-like receptor 4 (TLR4) signaling. TLR4 recognizes lipopolysaccharides that are common components of many Gram-negative and some Gram-positive bacteria and play a critical role in intestinal bacterial-host interactions (Abreu, 2010). Another study also noted that TCS treatment altered the expression of colonic proteins related with the maintenance of intestinal permeability, including ocludin, tight junction protein-1 (ZO-1), and mucin-3 (MUC3) (Yang et al., 2018). The study by Zhao et al. (2022) revealed that TCS exposure resulted in colitis in mice, mainly because specific gut microbial β-glucuronidase (GUS) homologs converted TCS to TCS-G. In zebrafish models, long-term exposure to high concentrations of TCS disordered the composition of the microbiota in the gastrointestinal tract and lessened its diversity (Tang et al., 2021). Furthermore, former studies proposed that the gut microbiome was necessary for the pro-inflammatory effect of TCS (Gao et al., 2017; Sanidad et al., 2022), and intestinal barrier dysfunction and intestinal microbiota disorder were associated with miR-21 (Johnston et al., 2018). Taken together, these

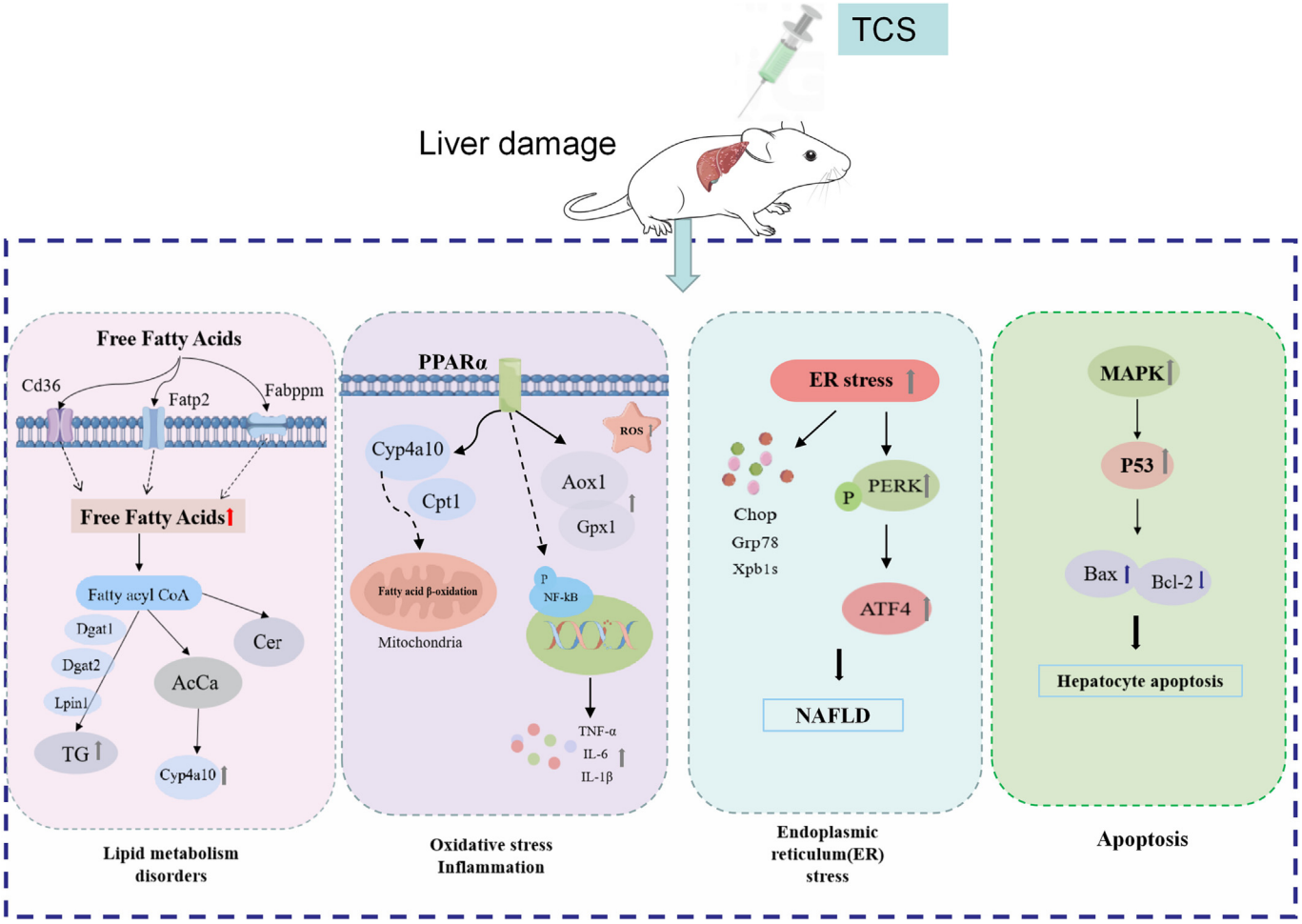

Fig. 2. A schematic model displayed the underlying mechanisms of TCS-mediated hepatic damage. TCS exposure impaired liver function predominantly via the lipid metabolism, oxidative stress, inflammation, endoplasmic reticulum stress, and hepatocyte apoptosis.

investigations above suggest that the detrimental effect of TCS on gut health may be related to the gut microbiome (Fig. 3), providing new mechanistic insights into TCS exposure and related diseases. In the future, we should pay more attention to the type and abundance of intestinal flora influenced by TCS exposure and then explore the biological significance.

5. Conclusion and prospect

Triclosan is a synthetic antimicrobial agent with a long history. In recent years, TCS has been considered as a novel endocrine disruptor and long-term exposure to TCS could have unfavorable effects on human health. Several in vivo and in vitro studies have suggested a possible association between TCS exposure and multiple adverse health outcomes, such as the impairment of reproductive function, disturbance in hepatic lipid metabolism, kidney damage, colitis, and so on. However, there is a relative lack of mechanism-based human studies in terms of number and scope, and most cohorts and in vitro studies have predominantly evaluated the toxic effects induced by TCS exposure, without in-depth dissection of the specific mechanisms of action and cellular targets of TCS. For example, recent studies have suggested that TCS could influence reproductive health and liver function by interfering with lipid metabolism (Huang et al., 2020; Zang et al., 2019), but these studies have not delved into the relevant microRNA gene expression that affects fatty acid synthesis and metabolism. In addition, a growing number of studies have indicated that TCS exposure disturbs intestinal flora homeostasis and has a carcinogenic potential (Wang et al., 2018c), but there are limited studies on how TCS perturbs intestinal flora homeostasis, and there is a serious lack of cohort studies based on population data. Consequently, there is a great need for further work to focus on the underlying mechanisms of action of TCS exposure and characterize its toxic effects in animal and cell models. With the current explosion of COVID-19, it is foreseeable that antimicrobial agents will be used in large quantities, and the safety of TCS is worth further discussing and verifying.

CRediT authorship contribution statement

Xuhui Chen: Methodology, Data collection, Writing - original draft.
Li Mou, Jiayuan Qu, and Liling Wu: Literature search, Data collection.
Changjiang Liu: Conceptualization, Funding acquisition, Writing - review & editing.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

None.

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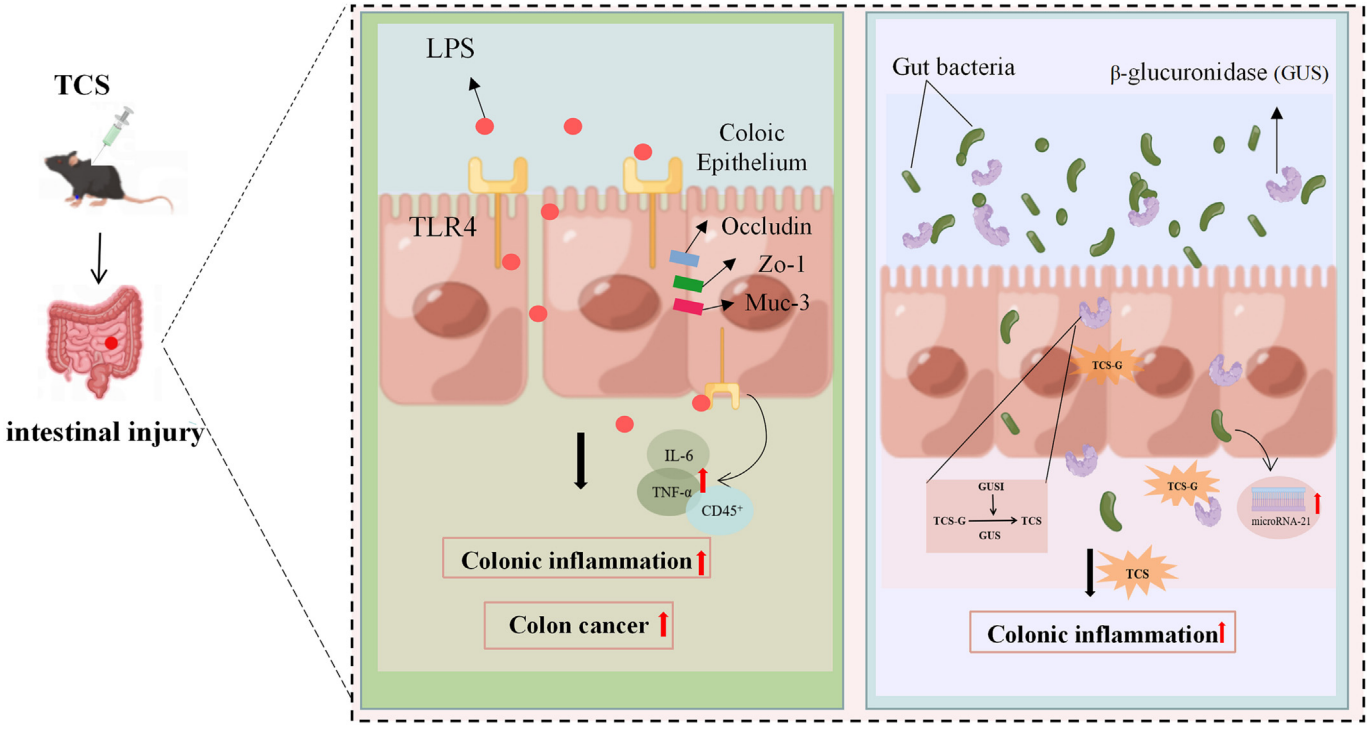

Fig. 3. A schematic model revealed that the possible mechanisms of TCS-caused intestinal injury. TCS treatment perturbed gut health through the induction of inflammation and the disorder of gut microbiome.

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