REVIEW ARTICLE

Adverse Effects of Pesticide Exposure on Gut Microbiome: Health Implications and Risks

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ABSTRACT

The gut microbiome plays a crucial role in human health, influencing various physiological processes. Exposure to environmental chemicals, particularly pesticides, has been shown to disrupt the balance of gut microbiota, leading to gut dysbiosis. This imbalance is associated with adverse health outcomes, including metabolic disturbances and chronic inflammation. However, scientific evidence on impacts of pesticides on gut microbiota and function remains limited. This review synthesizes recent findings on pesticide-induced gut dysbiosis, highlighting its significant health implications. Studies included in this narrative review were selected through a comprehensive search across multiple databases (PubMed, SCOPUS, Google Scholar, and ScienceDirect) covering from 2016 to 2025 using relevant keywords. Findings revealed that pesticides disrupt gut microbiota, affecting metabolism, gut barrier integrity, oxidative stress, and inflammatory responses in a dose- and duration-dependent manner. The review underscores the need for further research and cautious pesticide use to protect gut health.
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INTRODUCTION

A human being harbours 10–100 trillion microorganisms in the gastrointestinal tract. Out of the 70 known bacterial phyla in the microbiome, Bacteroidetes and Firmicutes were identified to be the major inhabitants comprising more than 90% of bacterial phylogenetic types [1]. In mammals, the gastrointestinal tract contains a diverse microbiome that varies physiologically in response to chemical and nutrient gradients, as well as localised immune responses, which shape the characteristics of the bacterial community [2]. A healthy and balanced gut microbiome is vital for human health and well-being. Its influence extends far beyond the gastrointestinal tract, impacting the brain via the gut-brain axis, and altering nearly every physiological process [3]. Alterations in gut microbial composition can affect host metabolism, and these changes can be influenced by many factors such as diet, lifestyle, use of antibiotics, age, host immunity, as well as geographical and environmental factors [4].

Environmental chemicals encompass a wide range of substances, both natural and synthetic, which are commonly applied in industrial activities, agricultural practices, and urbanisation. Pesticides, including insecticides, herbicides, and fungicides, warrant special attention due to their potential harm, as they are widely used for domestic and agricultural purposes. The impact of these chemicals is profound, affecting not only ecological systems but also human health which includes respiratory problem, reproductive issues and cancer risks [5–7]. Exposure to pesticides may negatively impact human health through gut dysbiosis. Recent findings have also highlighted the significant impact of environmental chemicals, including pesticide on gut microbial communities. These effects include decreased microbial diversity, altered community structure, and toxicity to non-target organisms, potentially contributing to disease development [8].

Dysbiosis in the gut occurs when there is an imbalance

in microbial communities, disrupting the normal function of beneficial microbiota essential for health and triggering processes that contribute to diseases [9, 10]. Health consequences that are linked with gut dysbiosis include inflammatory bowel disease, metabolic disorders and mental health issues [11, 12]. To explore these relationships, this review employed a comprehensive literature search using multiple databases (PubMed, SCOPUS, Google Scholar, and ScienceDirect) according to their relevance to the topic. This method ensured the inclusion of diverse and up-to-date research findings to critically assess the influence of pesticide exposure on gut microbial composition and its impact on human health. It is crucial to understand how the gut microbiome adapts and changes in response to these chemical exposures, as well as the potential health consequences stemming from such microbial shifts before the risks escalate further. This review specifically looks into the influence of pesticides exposure on gut microbial composition and its impact on human health.

The search strategy for identifying articles related to the research questions employed the Boolean Operators technique, using the following keywords: "pesticides" OR "pesticide exposure" OR "herbicides" OR "insecticides" combined with "gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "gut flora", and further refined with "glyphosate" OR "paraquat" OR "chlorpyrifos", as well as "adverse effects" OR "health risks" OR "dysbiosis" OR "gut health" OR "inflammatory response" OR "oxidative stress". The search was conducted across major databases including PubMed, SCOPUS, Google Scholar, and ScienceDirect. Filters were applied to include studies published from 2016 to 2025, written in English, and encompassing study types such as original research articles, reviews, and meta-analyses. This approach ensured a systematic and thorough retrieval of literature relevant to the adverse effects of pesticide exposure on the gut microbiome.

GUT MICROBIOTA: ROLES AND EFFECTS ON HUMAN HEALTH

The human gut microbiota encompasses the entire microbial population, including bacteria and other microorganisms, residing in the human gastrointestinal tract. Gut microbial population is primarily composed of Firmicutes, Proteobacteria, Bacteroidetes, and Actinobacteria, which comprises of key genera such as Bacillus, Bacteroides, Bifidobacteria, Clostridium, Enterococcus, Lactobacillus, Prevotella, and Ruminococcus [13, 14]. Each bacterial group plays a significant role in maintaining gut health and overall well-being.

The gut microbiota metabolizes dietary components into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which are crucial for regulating energy metabolism and supporting gut function. SCFAs, particularly butyrate, are vital for strengthening the intestinal barrier through tight junction proteins including zonula occludens (ZO) -1, which help maintain the integrity of the gut lining. Apart from their role in gut health, SCFAs also play a significant part in modulating immune responses. Butyrate, for instance, enhances the number and activity of regulatory T (Treg) cells, which are essential for maintaining immune tolerance and preventing excessive inflammation. Additionally, butyrate exerts anti-inflammatory effects by inhibiting the nuclear factor kappa-B (NF-κB) signalling pathway and stimulating the production of anti-inflammatory cytokines, such as interleukin-10 [15, 16].

In addition, the gut microbiome is also involved in bile acid metabolism, influencing lipid absorption and glucose homeostasis. These processes are regulated through signalling pathways involved with nuclear farnesoid X receptors (FXRs) and G-protein-coupled membrane receptors (GPCRs) [17]. Apart from bile acid metabolism, specific microbial genera also play distinct roles in dietary metabolism and SCFA production which further highlights the influence of gut microbiota on human health. For instance, Prevotella is associated with plant-rich diets and is crucial for carbohydrate fermentation in the gut. It often interacts synergistically with Ruminococcus to enhance fibre degradation and promote gut health [18]. This synergy involves production of cellulases and hemicelluloses, which break down complex carbohydrates into SCFA, highlighting the crucial role of gut microbiome interactions with its metabolites [19].

However, dysbiosis, or an imbalance in the gut microbiota, can disrupt these processes and has been linked to various health conditions. One key indicator of dysbiosis is an alteration in Firmicutes/Bacteroidetes (F/B) which can contribute to various metabolic and inflammatory conditions [20-22, 29]. For example, an increased F/B ratio is often linked to obesity [20, 21], as Firmicutes are competent in extracting energy from food, leading to more efficient calorie absorption and weight gain [22]. Conversely, a decreased F/B ratio is linked to inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn’s disease [23–25]. In these conditions, pathobionts like Bacteroidetes, particularly Bacteroides fragilis, can exacerbate inflammation by producing lipopolysaccharide (LPS) and pro-inflammatory cytokines [26]. Dysbiosis can also influence neurological functions through the gut-brain axis, as microbial metabolites impact mental health and have been implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as psychiatric conditions like anxiety and depression [27, 28]. This finding is further supported by a recent review highlighting that gut microbiome alterations, such as reduced microbial diversity, shifts in F/B ratios, and changes in SCFA-producing bacteria, are closely associated with the development and progression of

mental health disorders [29].

Additionally, it is also postulated that an imbalance in the composition of certain bacterial groups can also compromise the gut environment. For instance, Clostridium butyricum is beneficial for intestinal barrier support whereas other species within the same genus can have harmful effects. Notably, Clostridioides difficile and Clostridium botulinum are well-known pathogens responsible for severe conditions such as colitis and botulism, respectively [30]. These diseases arise from the production of potent toxins that disrupt cellular functions, damage tissues, and trigger inflammation [31, 32]. This highlights the importance of maintaining a balanced gut microbiota to prevent disease and support overall well-being.

Probiotic intervention, featuring beneficial bacteria such as Bifidobacterium, Lactobacillus, Enterococcus, and Bacillus, has shown protective effects against harmful bacteria like Proteobacteria and Verrucomicrobia [33–35]. These probiotics help enhance gut microbial diversity, improve digestion, and strengthen the immune system, ultimately promoting a balanced and resilient gut microbiome [36]. However, maintaining this balance can be challenging, especially in environments exposed to pollutants, such as pesticides, that were evidently shown to cause gut microbial imbalance and metabolic disruptions [37, 38]. Thus, it is crucial to understand the impacts of pollutants, including pesticides, on gut microbiota and potential health risks arising from the dysbiosis. Such insights could facilitate the development of targeted therapies, such as microbiota modulation or probiotics, and enable early detection through the identification of microbial biomarkers linked to pollutant exposure.

EFFECTS OF PESTICIDE EXPOSURE ON GUT MICROBIAL COMPOSITION

Glyphosate

Glyphosate, or N-(phosphonomethyl) glycine, is a non-selective systemic herbicide that inhibits the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). This enzyme is essential for the synthesis of aromatic amino acids in plants and microorganisms [39]. Due to the absence of this pathway in animals, glyphosate was initially considered as safe for non-target species. However, emerging research challenges this assumption. A dataset of EPSPS sequences derived from the core gut microbiome in humans revealed that approximately 54% of key species are sensitive to glyphosate [40], which raises concerns about its safety for humans and ecosystems.

Glyphosate exposure has been shown to significantly alter gut microbial composition, promoting dysbiosis across species, as reported in previous studies summarized in Table I. Out of nine studies reviewed, seven reported an increase in opportunistic bacteria

Table I: Summary of glyphosate's effects on gut microbial composition in animal studies.

Model/Species	Study objectives	Study design/sample	Main findings compared to control	Reference
Adult swiss mice	To study the impact of long-term low-dose GBH-RUp exposure on the gut morphology and microbial composition.	• The study involved groups of control and GBH-RUp-treated. • The treatment consisted of administering 0.075% w/v GBH-RUp in drinking water, beginning during pregnancy and continuing through to adulthood. • Various parameters were measured, including behavioral outcomes, intestinal morphology, and tight junction protein expression analysis, and microbiota analysis from faecal samples using 16S rRNA sequencing.	• Female mice: ↑ *Proteobacteria* and *Desulfobacteria.* • Male mice: ↓ *Bacteroidota.*	[41]
Earthworm (*Alma millsoni, Eudrilus eugeniae* and *Libyodrilus violaceus*)	To evaluate the effects of GBH on the gut microbiome of 3 different earthworm species.	• The study included control group and treatment group (RUp® Alphие) (n=60 earthworms per species). • The treatment involved applying 115.49 mL/m of RUp® Alphие, containing a glyphosate concentration of 7.2 g/L, over a period of 8 weeks. • The primary parameter measured was microbiota profiling from the earthworm's intestinal contents, analyzed using 16S rRNA sequencing.	• ↑ Proteobacteria. • ↑ *Enterobacteriaceae* and *Pseudomonadaceae.* • ↑ *Enterobacter* spp. *DHL-02, Pseudomonas putida, Pantoea agglomerans* and *Pseudomonas taiwanensis.* • ↓ alpha-diversity in exposed earthworms.	[42]
Sprague-Dawley rats	To investigate the lifelong and short-term effect of GBH on the gut microflora in mammals.	• The study consisted of control group and RUp-treated group (n=3 rats per group). • The treatment involved administering RUp GBH concentrations of 0.1 ppm, 400 ppm, and 5000 ppm in drinking water over a duration of 673 days. • Various parameters were measured, including microbiota analysis from stool samples using 16S rRNA sequencing, repetitive sequence-based PCR (rep-PCR), bacterial strain isolation, and in vitro culture to characterize resistance and tolerance against RUp.	Long-term exposure: • ↑ Bacteroidetes (*Muribaculaceae* (S24-7)). • ↓ *Lactobacillaceae.* Short-term exposure: • *Bifidobacteria, Clostridia,* and *Enterococci* were shown to be significantly inhibited at concentrations of 400 and 5000 ppm. • *Lactobacillus* showed resistance effects. • Coliforms showed susceptibility effects.	[44]

CONTINUE.....

Table I: Summary of glyphosate's effects on gut microbial composition in animal studies. (Continued....)

Model/Species	Study objectives	Study design/sample	Main findings compared to control	Reference
C57BL/6J mice	To study the potential of glyphosate to induce gut dysbiosis and a possible mechanism that adversely impacts host physiology. Specific objective: To study the changes in gut microbiome following glyphosate exposure in mice at different dosages.	• The study consisted of control group and three glyphosate-treated groups, (n=6 mice per group. • The treatment involved administering glyphosate via drinking water at concentrations of 1 µg/ml, 10 µg/ml, and 100 µg/ml for 90 days. • Several parameters were measured, including microbiota analysis from stool samples via shotgun metagenomic sequencing, immune cell analysis focusing on CD4+IL17A+ (Th17) cells, inflammatory markers, and pH levels.	10 µg/ml group: • *Lactobacillus reuteri* and *Bifidobacterium pseudolongum.* • ↑ *Bacteroides acidifaciens* 100 µg/ml group: • ↓ *Lactobacillus murinus, Lactobacillus sp. ASF360* and *Enterorhabdus mucosicola.*	[43]
Sprague-Dawley male rats	To study if glyphosate-mediated gut microbiota imbalance was a contributing factor to male reproductive toxicity.	• The study consisted groups of control, low-dose, and high-dose (n=18 rats per group, with three replicates of n=6 rats each). • The treatment involved oral feeding of glyphosate at doses of 10 mg/kg and 250 mg/kg body weight per day for 2 months. • Parameters measured included histopathological observations and IHC, microbiota analysis from intestinal contents via 16S rDNA sequencing, oxidative stress markers such as MDA, SOD, and inflammatory markers including (TNF-□, and IL-1□), and BTB integrity using the biotin tracer method.	• ↑ Bacteroidetes. • ↓ Firmicutes. • ↑ Prevotellaceae (Prevotella_1) and Bacteroidaceae (Bacteroides)	[47]
Adult honey bees	To study the impact of glyphosate exposure on the microbial profile and size in honey bee gut.	• The study included groups of control, G-5 and G-10 (n=15 bees per group). • The treatment involved feeding glyphosate-laced sugar syrup at concentrations of 5 mg/L and 10 mg/L for 5 days following reintroduction to the hive. • Gut contents were sampled for microbiota analysis, which was conducted using 16S rRNA sequencing. • In vitro experiments were also performed to assess bacterial colonization and susceptibility to infection in bacterial strains.	• ↓ *Snodgrassella alvi, Bifidobacterium,* and *Lactobacillus Firm-4* and *Firm-5* in both groups. • ↑ *Gilliamella apicola* in G-5 group.	[46]
Adult female Sprague-Dawley rats	To investigate the effects of glyphosate herbicide on gut microbiome in rats.	• The study consisted groups of control, glyphosate, and RUp MON 52276 groups, (n=12 rats per group). • Treatments were administered via drinking water at doses of 0.5 mg/kg, 50 mg/kg, and 175 mg/kg body weight per day for 90 days. • Parameters measured included shotgun metagenomic analysis of the caecal microbiome, pathway enrichment analysis, and metabolite analysis focusing on shikimate and 3-dehydroshikimate levels.	• ↑ *Eggerthella* isolate HGM04355, *Acinetobacter johnsonii*, and *Akkermansia muciniphila* • ↑ *Shinella zoogleoides.*	[48]
Zebrafish (*Danio rerio*)	To investigate the effects of microcystin-LR and glyphosate on zebrafish gut microbiome.	• The study included groups of MC-LR, glyphosate, and mixed MC-LR + glyphosate group, (n=45 zebrafish per group with three replicates). • The treatment consisted of exposure to 35 µg/L MC-LR and 3.5 mg/L glyphosate via their aquatic environment for 21 days. • Zebrafish intestines were collected for microbiota analysis, which was performed using 16S rRNA sequencing. • Additional parameters included histological analysis, measurements of cytokine levels, oxidative stress markers (MDA), intestinal mucosal markers, and inflammatory markers (IL-1β).	• *Fusobacteria*, Proteobacteria showed significant differences. • ↓ *Aeromonas, Mycobacterium, Tsukamurella* and *Vibrio* • ↑ *Metyhlobacterium* and *Pseudonocardia.*	[10]
Male Sprague-Dawley rats	To identify the gut microbial profile based on the antioxidant enzymes, morphology, levels of gene expressions and ion concentrations following glyphosate exposure.	• The study consists of control and glyphosate-treated group (n=8 rats per group). • Glyphosate was administered via oral gavage at doses of 5 mg/kg, 50 mg/kg, and 500 mg/kg body weight per day for 35 days. • Fresh stool samples were collected from treated rats for microbiota analysis. • Parameters measured included histological analysis, oxidative stress enzymes (SOD and MDA), cytokine expression (IL-1β, IL-6, and TNF-α), and gut microbiota composition through 16S rRNA sequencing	• ↑ *Fusobacteria, Ruminococcus_, Ruminococcaceae_NK4A214_group, Prevotella_1*, and *Prevotellaceae_UCG-003.* • ↓ Firmicutes and *Lactobacillus.*	[45]

BTB: blood-tissue barrier; CD4+IL17A+ cells (Th17): T-helper 17 cells producing IL-17A; GBH: glyphosate-based herbicide; GBH-RUp: glyphosate-based herbicide-RoundUp; IHC: immunohistochemistry; IL-1β: interleukin-1 beta; IL-6: interleukin-6; MDA: malondialdehyde; RUp: RoundUp; rDNA: ribosomal deoxyribonucleic acid; rRNA: ribosomal ribonucleic acid; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-alpha; ↑: increased; ↓: decrease

such as Proteobacteria and Bacteroidetes (e.g., Muribaculaceae, Bacteroidaceae, and B. acidifaciens) alongside a reduction in beneficial taxa like Lactobacillus, Bifidobacteria and Clostridia, which are particularly susceptible to glyphosate [41–47]. This disruption is driven from glyphosate's interference with the shikimate pathway, a critical process for aromatic amino acid synthesis in microorganisms. It is postulated that this interference can interrupt microbial metabolic symbiosis, impairing the production of menaquinols and phenolic compounds. These metabolic disturbances can lead to dysbiosis and its associated health implications [48].

Further studies have linked glyphosate-induced dysbiosis to elevated indicators of oxidative stress, including reactive oxygen species (ROS) and malondialdehyde (MDA) [47], as well as disruptions in serum metabolites involved in nicotinamide, branched-chain amino acids, methionine, cysteine, and taurine metabolism in which all are closely related to oxidative damage [49]. These biomarkers indicate excessive ROS production and impaired antioxidant defence systems, which can lead to cellular dysfunction. A similar condition has been observed with pro-inflammatory biomarkers, such as CD4+IL17A+ cells (Th17), which were found to be increased in glyphosate-treated subjects [43]. This increase in inflammatory markers has also been associated with the overgrowth of pathobionts, an opportunistic microorganism like Clostridioides difficile, which further exacerbates gut imbalance [50].

Additionally, glyphosate exposure has been shown to alter gut microbial composition differently across genders with distinct effects observed in males and females [41, 47]. In humans, gut microbial composition has been linked with sex hormone levels [51]. Disruptions in hormone regulation, which are often caused by endocrine-disrupting chemicals, can contribute to a range of diseases. These include diseases related to reproductive disorders, such as polycystic ovary syndrome and endometriosis, cardiovascular disorders, cancers, diabetes and obesity [52-54].

Glyphosate's impact on gut dysbiosis varies depending on dose and exposure duration [42, 44]. A recent study has shown that low-dose glyphosate exposure over 30 days particularly affects Lactobacilli, while also increasing the abundance of opportunistic bacterial groups like Proteobacteria and Bacteroidetes. Similarly, high-dose of glyphosate treatment (7.2 g/L applied on 115.49 mL/m area) over 8 weeks reported results of increased opportunistic bacterial groups (Proteobacteria and Enterobacteriaceae), while reducing alpha-diversity in gut contents of exposed earthworms [42]. Even more prolonged duration of exposure (>1 year) of high-dose glyphosate, ranging from 400 to 5000 ppm in drinking water, demonstrated an inhibition of beneficial bacteria, such as Bifidobacteria and Clostridia [44].

European Food Safety Authority (EFSA) and European Union Member State experts have established critical safety thresholds for glyphosate to guide its use and minimize health risks. These include an acute reference dose (ARfD) for glyphosate at 0.5 mg/kg body weight, marking the first time such an exposure threshold has been applied to glyphosate. Additionally, they set an acceptable operator exposure level (AOEL) of 0.1 mg/kg body weight per day and an acceptable daily intake (ADI) of 0.5 mg/kg body weight per day, aligning with the ARfD [55]. As a result, while glyphosate provides significant agricultural benefits, its potential adverse effects on gut microbiota, contributing to resistance development, and posing health risks demand careful consideration and further research. Balancing these factors is crucial for ensuring sustainable farming practices and safeguarding public health, as well as underscoring the need for continued research and informed decision-making.

Paraquat

Paraquat is a highly toxic, nonselective herbicide linked to significant deaths in both humans and animals. When ingested, it can trigger multisystem organ failure, primarily due to the formation of ROS caused by the inhibition of NADH reduction to NADPH [56, 57]. Moreover, paraquat exposure has been shown to induce behavioural and metabolic changes, as well as cellular damage attributed to oxidative stress [58]. Its potent oxidative stress-inducing properties may impact host tissues and disrupt the delicate balance of the gut microbiota.

Studies on the effects of paraquat on gut microbial composition, as presented in Table II, demonstrated a trend of reduced beneficial taxa such as Firmicutes, Lactobacillus, Bifidobacterium pseudolongum, and families like Lachnospiraceae and Ruminococcaceae. This disruption impairs key functions, including fermentation of dietary fibres and production of SCFAs, while favouring the growth of pathogenic microbes, such as Escherichia coli and Bacteroides, which are linked to inflammation and gut barrier dysfunction. The increased presence of these pathogenic taxa correlates with an upregulation of inflammatory cytokines, such as IL-1β and inducible nitric oxide synthase (iNOS), in animal models [59], intensifying both gut inflammation and systemic inflammatory responses. These inflammatory cascades activate immune cells, leading to the formation of ROS and reactive nitrogen species (RNS), which further exacerbate oxidative stress [60].

A recent study further supports these findings, demonstrating that paraquat exposure alters gut microbial composition by increasing Bacteroidetes while reducing beneficial taxa such as Ruminococcaceae, Lactobacillus, and species like Eubacterium coprostanoligenes and L. amylovorus, leading to gut dysbiosis [61]. In addition, paraquat induces oxidative stress, as shown by reduced

Table II: Summary of paraquat's effects on gut microbial composition in animal studies.

Model/Species	Study objectives	Study design/sample	Main findings compared to control	Reference
C57BL/6 mice	To investigate the effect of paraquat exposure to the gut microbial composition in adult mice.	• The study included two groups: a control group (n=33) and a paraquat-treated group (n=39). • The treatment consisted of 0.8 mg/kg body weight per day administered via intraperitoneal injection from postnatal day 5 to postnatal day 19. • Caecal samples were collected from both groups for microbial analysis. • Parameters measured included changes in body weight, microbiota analysis of caecal samples via 16S rRNA sequencing, and functional gene measurements related to carbohydrate, energy, lipid, amino acid, and glycan biosynthesis.	• ↓ Firmicutes • ↑ Cyanobacteria	[65]
A53T-L444P and A53T mice	To investigate the impact of chemical exposure in combined with radiation on behavioural changes and gut dysbiosis in mice.	• The study involved a control group and a treatment group (paraquat and DSS radiation), with a total of 313 subjects employed across four different studies. • The treatment involved administering paraquat at a dose of 10 mg/kg twice a week via injection for 3 weeks. • Faecal samples were collected from all groups for microbiome testing. • Parameters measured included behavioural tests, cognitive tests, sensorimotor function assessments, and microbiome analysis via 16S rRNA sequencing.	• ↑ *Bacteroides*. • ↓ *Lactobacillus*.	[64]
Wistar rats	To study the changes in gut microbial composition following paraquat exposure.	• The study consisted groups of control and two paraquat-treated groups (PQ-15 and PQ-30), n=10 per group. • The treatment involved intraperitoneal injections of paraquat at doses of 15 mg/kg and 30 mg/kg body weight per day for 3 days. • Parameters measured included body weight changes, histological analysis, oxidative stress markers (MDA, SOD, ROS, and 8-isoprostanes), inflammatory markers (MCP-1), and microbiota profiling of caecal samples via shotgun metagenomics sequencing.	• Abundance in *Escherichia coli* and *Akkermansia muciniphila*. • *Bifidobacterium pseudolongum*, *Lactobacillus johnsonii*, *Akkermansia muciniphila*, and *Escherichia coli* showed significant associations. • ↓ Alpha diversity.	[66]
C57BL/6J mice	To evaluate the impact on gut dysfunction following paraquat exposure.	• The study included a control group and a paraquat-treated group, n=10 rats per group. • The treatment involved intraperitoneal injections of paraquat at a dose of 15 mg/kg body weight, administered twice a week for 8 weeks. • Faecal samples were collected from all groups for microbial analysis. • Other parameters measured included neurobehavioural tests, intestinal epithelial barrier function (ZO-1 and occludin), SCFA metabolism, and inflammatory markers (CD11b, IL-1β, iNOS, and HMGB1).	• ↓ *Lachnospiraceae*, *Prevotellaceae*, *Rikenellaceae*, and *Ruminococcaceae*. • ↑ *Bacteroide*s.	[59]

CD11b: Cluster of differentiation molecule 11B; DSS: Dextran Sulphate Sodium; HMGB1: High Mobility Group Box 1; IL-1β: Interleukin-1 beta; iNOS: inducible Nitric Oxide Synthase; MDA: malondialdehyde; MCP-1: Monocyte Chemoattractant Protein-1; PQ: paraquat; ROS: Reactive Oxygen Species: ROS; rRNA: ribosomal Ribonucleic Acid; SCFA: Short-chain Fatty Acids; SOD: Superoxide Dismutase; ZO-1: Zonula Occludens-1; ↑: increased; ↓: decrease

hepatic activities of SOD and GSH-Px, elevated MDA levels, and downregulated antioxidant gene expression. This oxidative damage is accompanied by increased inflammation, marked by a rise in hepatic CD3+ T cells and CD68+ macrophages, highlighting the compound's multifaceted impact on gut health, oxidative balance, and inflammatory responses [61]. Paraquat exposure also amplifies oxidative damage through lipid peroxidation, compromising cell membrane integrity, as shown by elevated extracellular lactate dehydrogenase activity [62]. This condition may contribute to the onset and progression of degenerative diseases, including cancer, neurological disorders, psychiatric conditions, and aging [63].

It is postulated that microbial shifts induced by paraquat exposure may have significant implications for brain health [64]. For instance, a study by Chaklai et al. demonstrated that an increased abundance of pathogenic taxa is associated with altered behavioural performance, potentially exacerbating neurodegenerative processes, such as those observed in Parkinson's disease [64]. Another study also shows that early-life paraquat exposure disrupts gut microbiota in a sex-dependent manner, with male mice exhibiting significant microbial alterations, while female mice were unaffected [65]. This indicates that females may possess a greater resistance to paraquat's effects compared to males and dysbiosis in microbial composition may influence obesity development.

Furthermore, the effects of paraquat exposures on gut microbiota also depend on dose and duration of exposures. For example, a study by Hernandez-Baixauli et al. [66] reported that short-term treatment (3 days) with both low and high doses of paraquat (15 mg/kg and 30 mg/kg) led to reduced alpha diversity and an increase in potentially pathogenic species like Escherichia coli, which correlated with increased isoprostane levels, a biomarker of oxidative stress. Similarly, another study demonstrated microbial shifts linked to altered gut metabolism and weight gain following 5 days of low-dose

paraquat intervention [65]. In contrast, a higher dose (15 mg/kg) administered for 8 weeks caused disruptions in intestinal barrier function and increased inflammation [59]. According to the latest technical report of paraquat toxicology, the ADI and ARfD for paraquat remain at 0.004 mg/kg body weight, as established by EFSA [67]. Balancing between agricultural purposes and maintaining public and environmental health is essential for sustainable practices and informed risk management.

Chlorpyrifos

Chlorpyrifos is a synthetic and non-selective insecticide widely used to target pests, but it poses risks to various life forms, even at low concentrations. Although it is designed to be safe for the environment, chlorpyrifos can have unintended impacts on ecosystems and living organisms [68, 69]. Its mechanism of action involves the inhibition of acetylcholinesterase after being metabolized by the cytochrome P450 enzyme. This leads to the accumulation of acetylcholine, causing excessive stimulation of cholinergic synapses in the nervous system [70]. It is hypothesized that this neurotoxic effect may disrupt the gut-brain axis, potentially contributing to gut dysbiosis. This effect is supported by previous studies, as summarised in Table III, which have documented dysbiosis in gut microbiota following chlorpyrifos exposure.

According to previous studies, chlorpyrifos-induced dysbiosis has been associated with altered lipid profiles and inflammatory responses. For instance, a study on chronic perigestational exposure to chlorpyrifos revealed changes in gut microbiota, accompanied by altered body weight, blood glucose levels, and lipid markers. These alterations are linked to metabolic disruptions, increasing the risks of growth retardation, obesity and type 2 diabetes [71]. Similarly, chlorpyrifos exposure also induced short-term changes in gut microbial composition at the genus and species levels, as well as long-term metabolic effects which include hyperlipidemia, hypoglycemia, and reduced cellular energy production [72]. Together, these findings underscore that chlorpyrifos-induced dysbiosis not only alters gut microbiota composition but also plays a significant role in driving metabolic disruptions.

Furthermore, another study on chlorpyrifos exposure reported results of reduction in the levels of tight junction proteins (e.g., occludin, claudin 1, and ZO-1), alongside an upregulation in the expression of pro-inflammatory mediators (e.g., TNF-α, MCP-1, IL-1 β, PAI-1), of which both increase inflammation and impair gut barrier [72]. In addition, alterations in gut microbiota were observed, with a notable increase in Clostridium

Table III: Summary of chlorpyrifos's effects on gut microbial composition in animal studies.

Model/ Species	Study objectives	Study design/sample	Main findings compared to control	Reference
Male Wistar rats	To study DEP effects, including CPF, on hormones and gut microbiota in rats.	• The study involved three groups: a control group, a low-dose group (DEP-L), and a high-dose group (DEP-H), n=10 rats per group. • DEP was administered via oral gavage at doses of 0.8 and 0.13 mg/kg body weight/day for 20 weeks. • Parameters measured included body weight changes, lipid profiles, hormones, and inflammatory markers (IL-6, MCP-1, and TNF-α), microbiota analysis from stool samples was analyzed using 16S rRNA sequencing.	• ↑ *Adlercreutzia, Alloprevotella, Bacteroides, Clostridium sensu stricto 1, Eubacterium ventriosum* group, *Helicobacter, Intestinimonas, Lactobacillus, norank f Erysipelotrichaceae, Parabacteroides*, and *Paraprevotella.* • ↓ *Candidatus Saccharimonas, Candidatus Soleaferrea, Catabacter, Defluviitaleaceae UCG-011, Eubacterium xylanophilum* group, *Erysipelatoclostridium, Faecalibaculum, Jeotgalicoccus, Mucispirillum, norank f Christensenellaceae, Parasutterella, unclassified f Peptostreptococcaceae, Ruminococcaceae_UCG-014*, and *Ruminococcaceae_UCG-004.*	[74]
Male Wistar rats	To investigate the effects of CPF exposure on rat gut microbial profile.	• The study included a control group, a low-dose group (0.3 mg/kg CPF), and a high-dose group (3 mg/kg CPF), n=6 rats per group. • CPF was administered via oral gavage daily for 9 weeks. • Parameters measured included glucose tolerance, lipid profiles, cytokines, and microbiome profiling from faecal samples using 16S rRNA sequencing.	In normal-fat and CPF-treated rats: • ↑ *Allobaculum, Anaeroplasma, Candidatus, Coprococcus, Roseburia*, and *Sutterella.* • ↓ *Aerococcus, Anaerosporobacter, Brevundimonas, Pseudoflavonifractor*, and *Trichococcus.* In high-fat rats and CPF-treated rats: • ↑ *Acinetobacter, Blautia, Candidatus, Oscillibacter*, and *Sutterella.* • ↓ *Alloprevotella, Amphibacillus, Clostridium sensu stricto, Enterorhabdus, Hydrogenoanaerobacterium, Olsenella*, and *Ruminococcus.*	[79]
Wistar rats	To assess the impact of perigestional exposure to CPF on the metabolic regulation of mother rats and their female offspring during early adulthood.	• The study consisted of three groups: a control group, a CPF group (1 mg/kg CPF), and a CPF + inulin group with n=4 dams and n=6–10 offspring per group. • CPF was administered daily via oral gavage for 4 months. • Microbiota samples were obtained from intestinal contents, and parameters measured included body weight changes, lipid and glucose profiles, bacterial translocation, microbial metabolites, and microbiota profiling using a culture-based approach.	• ↓ *Bifidobacterium, Lactobacillus* • ↑ *Staphylococcus* and *Clostridium* After inulin supplementation: • ↑ *Lactobacillus* • ↓ *Staphylococcus, Clostridium* and *Enterococcus*	[71]

CPF: Chlorpyrifos; DEP: Diethylphosphate; MCP-1: Monocyte Chemoattractant Protein-1; MPO: Myeloperoxidase; ribosomal Ribonucleic Acid: rRNA; TNF-α: Tumour Necrosis Factor-α; ↑: increased; ↓: decreased

spp. and Enterococcus spp. in pregnant women exposed to chlorpyrifos. This shift was accompanied by compromised gut barrier integrity, as evidenced by increased fluorescein isothiocyanate dextran (FD4) permeability [73]. These findings suggest that chlorpyrifos, once metabolized by gut bacteria, weakens gut barrier function, further exacerbating intestinal permeability and inflammation. This underscores the compound's potential to disrupt both microbial balance and gut integrity, contributing to systemic health risks.

Chlorpyrifos exposure has been shown to exert dose- and duration-dependent effects on gut microbial composition across various animal studies. For example, diethylphosphate (DEP), a non-specific metabolite of organophosphates like chlorpyrifos, showed effects on gut microbiota, serum hormones, and pro-inflammatory cytokines like interleukin-6 (IL-6) following long-term and high-dose exposure (0.13 mg/kg of DEP for 20 weeks). These effects suggest possible systemic inflammation and endocrine-disrupting properties [74, 75]. Similarly, a study on rat pups reported that chronic exposure to low-dose chlorpyrifos led to microbial dysbiosis at the weaning stage, indicated by an increase of potentially harmful bacteria [76]. These findings are aligned with previous research on chlorpyrifos-induced gut dysbiosis in offspring or humans at a young age, leading to neurodevelopment impairment [77, 78]. Another study on chronic exposure to chlorpyrifos also showed results of an increase in bacterial groups linked to neurotoxicity and islet injury, alongside a notable drop in serum insulin and amylin levels, particularly at low doses. This indicates pancreatic dysfunction and impaired glucose regulation, potentially leading to the development of diabetes, obesity, and metabolic disorders [79, 80].

The progressive reduction of chlorpyrifos' ADI by the EFSA has led to a maximum residue level (MRL) of 0.01 mg/kg in food. Monitoring data from 2016 onwards confirmed a significant drop in exposure levels, demonstrating the effectiveness of these regulatory measures in safeguarding public health [81]. However, despite that, previous findings highlight the dose-dependent nature of chlorpyrifos-induced dysbiosis and its strong associations with metabolic and inflammatory diseases. This highlights the ongoing need for stricter pesticide regulations and further research to fully understand and mitigate the long-term health risks posed by chlorpyrifos exposure.

Other pesticides

Insecticides such as diazinon, chlorfenapyr, acetamiprid, coumaphos, tau-fluvalinate, oxalic acid, dichlorodiphenyldichloroethylene, and β-hexachlorocyclohexane, and the fungicide chlorothalonil pose significant risks to host health and overall physiology. These pesticides can persist in the environment, particularly in sediments, creating long-term exposure risks for organisms in the affected area [82–86]. Exposure to these pesticides is known to cause changes in the gut microbiota, thereby disrupting microbial diversity, inhibiting microbial function, affecting specific bacterial taxa and altering metabolic pathways [87–91]. The changes in microbial composition induced by these pesticides are summarized in Table IV.

For example, diazinon exposure caused significant, sex-specific alterations in gut microbiota, as shown by 16S rRNA gene sequencing, shotgun metagenomics, and metabolomics profiling. These findings revealed a reduction in SCFA-producing bacteria (Lachnospiraceae), alongside an increase in potentially pathogenic bacteria (Burkholderiales). In male mice, these changes were accompanied by reduced body weight and a decreased F/B ratio [92]. This diazinon-induced dysbiosis, acetylcholinesterase inactivation, and oxidative stress, can lead to widespread cellular and systemic damage. Diazinon generates toxic oxygen analogue metabolites during oxidative activation, which produce free oxygen radicals, causing oxidative DNA damage, DNA instability, and localized apoptosis [93-94]. A recent study further highlights that diazinon not only induces oxidative damage but also triggers pro-inflammatory responses, contributing to health conditions such as nephrotoxicity, histopathological impairment, and dysfunction in multiple organs [94].

Meanwhile, chlorfenapyr exerts its effects through its active metabolite, tralopyril, which disrupts adenosine triphosphate synthesis, leading to cell death [95]. On the other hand, acetamiprid targets nicotinic acetylcholine receptors, causing paralysis and death in insects [96]. Despite that, both pesticides have been shown to affect mammals by altering intestinal microbial diversity, increasing oxidative stress, and triggering pro-inflammatory responses. These changes disrupt the interaction between the host microbiome and its metabolites [91, 97]. Acetamiprid-induced dysbiosis, characterized by elevated oxidative stress and inflammation, may explain its association with health issues such as upregulation of apoptosis-related genes, impaired reproductive systems, and neurological symptoms [98, 99]. In light of these potential risks, the EFSA has proposed lowering the ADI and ARfD for acetamiprid from 0.025 mg/kg body weight to 0.005 mg/kg body weight per day, reflecting the need for stricter regulatory measures to safeguard public health [100].

Another study also reported microbial dysbiosis following exposure to chlorothalonil, tau-fluvalinate, and coumaphos. Tau-fluvalinate exposure led to an increase in Enterobacteriaceae and Caulobacteraceae, while chlorothalonil exposure resulted in a decrease in Lactobacillus [101]. Previous studies have also demonstrated significant neurotoxic effects of tau-fluvalinate and coumaphos, including alteration in xenobiotic metabolism, oxidative stress, and DNA

Table IV: Summary of other pesticides' effects on gut microbial composition in animal studies.

Model/ Species	Study objectives	Study design/sample	Main findings compared to control	Reference
C57BL/6 mice	To evaluate the gut microbial structure and metabolic profiles following the exposure of diazinon in mice.	• The study consisted of two groups: control group and diazinon-treated group (n=10 mice per group, with 5 males and 5 females each). • Diazinon was administered via drinking water at a dose of 4 mg/L for 13 weeks. • Faecal samples were collected for microbiota analysis. • The parameters measured included 16S rRNA gene sequencing, metagenomics sequencing, and metabolomics profiling to assess the impact of diazinon exposure.	• *Bacteroides*, *Coprobacillus*, and two unidentified genera under family *Burkholderiales* and *Clostridiaceae*. • *Butyrivibrio*, *Shuttleworthia*, and *Staphylococcus* growth were repressed.	[92]
Kunming mice	To study the impact of pesticide chlorfenapyr and acetamiprid on gut microflora and metabolic functions.	• This study included four groups: a control group, a chlorfenapyr group, an acetamiprid group, and a combined treatment group, (n=4 mice per group). • Chlorfenapyr (0.18 mg/kg), acetamiprid (3.15 mg/kg), and the combined dose (3.15 + 0.18 mg/kg) were orally administered daily for 90 days. • Faecal samples were collected for microbiota analysis. • The study parameters included 16S rRNA sequencing, metabolomics analysis, inflammatory marker evaluation, and intestinal health assessments.	Chlorfenapyr: • ↑ *Butyricimonas*, *Desulfovibrio*, *Helicobacter*, *Intestinimonas*, *Lachnoclostridium*, *Oscillibacter*, *Roseburia*, and *Ruminiclostridium*. • ↓ *Alloprevotella*, *Bacteroides*, *Enterococcus*, *Enterorhabdus*, *Erysipelatoclostridium*, *Lactobacillus*, and *Parasutterella*. Acetamiprid: • ↑ *Marvinbryantia*. • ↓ *Parabacteroides*, *Muribaculum*, and an unknown_Clostridiales genus.	[91]
Honey bees (*Apis mellifera*)	To study the impact of pesticides (chlorothalonil, coumaphos, and *tau*-fluvalinate) in field-level on gut microbial structure in honey bee.	• The study was conducted on four groups: a control group, a coumaphos group, a tau-fluvalinate group, and a chlorothalonil group. • Coumaphos and tau-fluvalinate were administered using two impregnated strips per hive for six weeks, while chlorothalonil was provided at 10 µg/L in a 30% sucrose solution for the same duration. • DNA was extracted from pooled gut samples of five bees per replicate for microbiota analysis. • Parameters measured included 16S rRNA sequencing, ITS sequencing, and functional inference using PICRUSt to evaluate microbiota composition and functionality.	Chlorothalonil: • ↓ Lactobacillales Coumaphos: • ↑ Burkholderiales and Bifidobacteriales. • Significant changes of Rhodocyclales. *Tau*-fluvalinate: • ↑ Enterobacteriales and Caulobacterales	[101]
Honey bees (*Apis mellifera*)	To investigate the changes in gut microbiome following the exposure of pesticides (acetamiprid, oxalic acid, and thiacloprid) in honey bees.	• This study included a control group and treatment groups exposed to acetamiprid, thiacloprid, or oxalic acid via sugar water. • Bees were exposed to acetamiprid (3.5 µg/ml), thiacloprid (0.05 µg/ml), and oxalic acid (1750 µg/ml) for seven days. • Gut samples were dissected from three bees per sub-colony, with a total of 146 bees sampled for analysis. • The parameters measured included 16S rRNA amplicon sequencing, microbial richness analysis, beta diversity analysis, and microbial network analysis.	Oxalic acid: • *Bombella apis* and *Lactobacillus* Firm-5 were inhibited at highest concentration. • ↑ *Bartonella*, *Bifidobacterium*, *Commensalibacter*, *Frischella*, *Gilliamella*, *Lactobacillus*, *Snodgrassella*. • ↓ *Bombella*.	[105]
C57BL/6 mice	To study the effects of p, p'-DDE and β-HCH on intestinal microbiome, bile acid profile and metabolism in mice.	• The study involved three groups: a control group, a p,p'-DDE group (1 mg/kg), and a β-HCH group (10 mg/kg), (n=8 mice per group). • Pesticides were administered daily via oral gavage for eight weeks. • Faecal samples were collected from the distal colon for microbiota analysis. • Parameters measured included 16S rRNA sequencing for microbiota profiling, bile acid profiling using UPLC-MS, and expression analysis of genes related to bile acid metabolism.	• ↑ Proteobacteria (β-proteobacteria), Firmicutes, Bacillales, Bifidobacteriales, Burkholderiales, Campylobacterales, and Verrucomicrobiales, *Akkermansia*, *Alloprevotella*, *Barnesiella*, *Lactobacillus*, *Oscillibacter*, and *Parasutterella*. • ↓ in Bacteroidales, Lactobacillales and Oceanospirillales, Actinobacteria, Bacteroidetes, *Candidatus Saccharibacteria*, Verrucomicrobia, Bacteroidia, Bacilli, *Bacteroides*, *Clostridium XIVa* and *Clostridium IV*, *Prevotella*, and *Parabacteroides*.	[90]

DNA: Deoxyribonucleic Acid; β-HCH: beta-Hexachlorocyclohexane; ITS: Internal Transcribed Spacer; P, p'-DDE: P, p'-Dichlorodiphenyldichloroethylene; PICRUSt: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; rRNA: ribosomal Ribonucleic Acid; UPLC-MS: Ultra-Performance Liquid Chromatography-Mass Spectrometry; ↑: increased; ↓: decreased

damage. These effects arise from their shared ability to disrupt acetylcholinesterase in the nervous system and interfere with cellular signalling pathways [102, 103]. Meanwhile, chlorothalonil exerts its toxicity by binding to cysteine-containing proteins, disrupting their function, and blocking glycolysis and respiration pathways. This mechanism has been linked to health risks such as cancer, reproductive disorders, kidney injury, and diabetes in humans [104]. These conditions are postulated to result from the pesticide-induced imbalances that affect metabolism, immune pathways, and cellular signalling.

The effects of these pesticide exposure are demonstrated in a dose and duration-specific manner. For instance, a study investigating various dosages of pesticides, including acetamiprid, oxalic acid, and thiacloprid, revealed that only oxalic acid caused a microbial shift compared to controls, highlighting its potential dose-dependent effects [105]. Similarly, diazinon was also reported to induce oxidative stress and pro-inflammatory effects in the kidney and testes in a dose-dependent manner [93]. Another study involving high doses of thiacloprid (0.6 mg/L and 2.0 mg/L) demonstrated gut dysbiosis, which resolved by day 13, indicating the

presence of duration-dependent effects [106]. These findings emphasize that both the dose and duration of pesticide exposure play critical roles in determining their impact on gut microbiota. This highlights the need to carefully assess exposure levels and recovery timelines in future studies.

LIMITATIONS AND SUGGESTIONS

Most research relies on animal models, which may not accurately represent the human gut microbiome. Additionally, studies often employ high-dose and short-term exposure scenarios that do not reflect actual conditions, where low-dose and long-term exposures, which are more relevant, have been less thoroughly investigated. Furthermore, most studies focus on short-term changes in gut microbiota, with limited understanding of the long-term health impacts, including chronic diseases. Variations in study methods, including differences in sequencing techniques and microbiota sampling protocols, complicate cross-study comparisons. While this narrative review offers a broad synthesis of existing evidence, it does not follow a registered protocol or systematic search strategy. For instance, this article did not explore key aspects of the 16S rRNA sequencing methodology, including DNA extraction procedures, primers used for PCR amplification, the selection of sequencing platforms, bioinformatics pipelines, and reference databases. A systematic review evaluating the variability and impact of these methodological choices on microbiome profiling outcomes would be valuable to guide future research, promote standardisation, and reduce bias. Individual factors, such as sex, age, and genetics, are also frequently overlooked. Moreover, relatively few studies examine the combined effects of multiple pesticide exposures, which are common in real-life scenarios.

To build upon the strengths of this review and enhance its relevance and applicability, several additional aspects could be explored. These include focusing on realistic exposure scenarios, expanding research to human studies across diverse populations, exploring understudied pesticides and their associations with microbial imbalances and diseases, as well as investigating potential interventions such as probiotics and dietary modifications.

CONCLUSION

Exposure to various pesticides, such as glyphosate, paraquat, chlorpyrifos, insecticides, and fungicides, disrupts the balance of gut microbial communities, and the effects appear to be dose-dependent. This contributes to systemic health issues such as inflammation, oxidative stress, metabolic disturbances, and potential links to diseases like obesity, diabetes, and neurological disorders. Understanding their involvement in disease pathogenesis may help in developing strategies in the public health protection and disease prevention. In addition, future systematic reviews should aim to offer a more comprehensive and impartial synthesis of the existing evidence, ensuring a balanced understanding of this important topic.

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