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Review Article

Exploring the role of polysaccharides in mitigating organ damage caused by pesticide-induced toxicity: A systematic review and meta-analysis of in vivo studies

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Abstract

Although polysaccharides have demonstrated potential in alleviating dysbiosis, the overall impact of polysaccharides on minimizing oxidative stress and organ damage in vivo has not been thoroughly investigated. The aim of this study was to investigate the comprehensive effects of polysaccharides in mitigating pesticide toxicity in animal studies, focusing on biomarkers related to oxidative stress, antioxidant activity, kidney injury, lipid profiles, liver function, and the preservation of liver and kidney weights. A systematic search was conducted across nine indexed databases, including PubMed, Cochrane CENTRAL, Taylor & Francis, Scopus, Sage, EBSCO, ProQuest, ScienceDirect, and Google Scholar. Rayyan.ai was used to screen in vivo studies that met the predefined inclusion and exclusion criteria. The quality of the selected in vivo studies was evaluated using SYRCLE's Risk of Bias tool, specifically designed for animal studies. Thirteen randomized animal studies, comprising 330 mice and rats, were included in the analysis. The findings revealed that polysaccharides significantly increased antioxidant levels, including catalase (CAT) (p<0.00001), superoxide dismutase (SOD) (p<0.00001), glutathione peroxidase (GPx) (p<0.00001), and reduced glutathione (GSH) (p<0.00001). Polysaccharides also significantly reduced oxidative stress markers, such as malondialdehyde (MDA) (p<0.00001) and nitric oxide (NO) (p<0.0001), as well as kidney injury biomarkers, including serum creatinine (p<0.00001) and urea (p<0.00001). Additionally, improvements in lipid profiles were observed, with significant reductions in triglycerides (TG) (p=0.04) and total cholesterol (TC) (p<0.00001). However, there were no significant differences in high-density lipoprotein (HDL) (p=0.28) and low-density lipoprotein (LDL) (p=0.32) levels. Polysaccharides significantly alleviate liver biomarkers, including aspartate transaminase (AST) (p<0.0001), alanine transaminase (ALT) (p<0.005), and alkaline phosphatase (ALP) (p<0.0001). Polysaccharides also contributed to the maintenance of liver weight (p=0.009), although no significant differences were observed in kidney weights (p=0.81). The study highlights that polysaccharides exert significant effects in enhancing antioxidant levels, reducing oxidative stress and organ damage biomarkers, and preserving liver weights.

Keywords: Dysbiosis, gut microbiota, pesticide, polysaccharides, oxidative stress

Introduction

Synthetic pesticides pose serious health risks to agricultural workers globally [1]. Exposure to synthetic pesticides induces oxidative stress, leading to systemic inflammation and organ

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damage, particularly affecting the kidneys and liver [2]. Chronic kidney disease (CKD) is prevalent among agricultural communities, with 18.6% of rice farmers in West Java, Indonesia, affected by CKD of unknown etiology [3-5]. Kidney failure rates are expected to rise, with treatment costs projected at 7–10 trillion Indonesian Rupiah by 2025 [6]. Similarly, pesticide exposure contributes to liver damage, with a significant prevalence of liver fibrosis (14.4%) in rural farming communities, associated with metabolic risk factors influenced by pesticide exposure [7]. In Indonesia, 67.4% of farmers report liver dysfunction, correlated with duration of employment and frequency of pesticide use [8], underscoring the frequent occurrence of pesticide exposure-induced organ damage in agricultural communities. However, treatment for pesticide-induced organ damage remains inadequate in Indonesia [9].

Organ damage from pesticide exposure occurs through the dysbiosis pathway [10]. Chronic dietary pesticide exposure alters the intestinal flora, leading to metabolic disorders, inflammation, and organ dysfunction [11]. Exposure to pesticides through food and the environment has been shown to alter intestinal microflora composition by reducing species diversity and shifting the proportions between bacterial groups [11]. These changes include a reduced *Bacteroidetes*-to-*Firmicutes* ratio and an increase in gram-negative bacteria, such as *Enterobacteriaceae*, which elevate systemic inflammation through lipopolysaccharide endotoxins [12]. Pesticides are toxic to intestinal microbiota, disrupting the growth of bacteria that protect the intestinal barrier [13]. Disturbances in intestinal microflora allow pathogenic bacteria to trigger excessive immune responses, producing pro-inflammatory cytokines and increasing oxidative stress, which subsequently affects organ function [11].

Polysaccharides have been shown to inhibit microbial dysbiosis, reduce chronic inflammation, and modulate gut permeability in high-fat diet-induced dysbiosis [14]. A previous study found that polysaccharides aid recovery from antibiotic-induced dysbiosis by restoring beneficial gut flora, reducing endotoxemia and pro-inflammatory cytokines, and repairing gut barrier integrity in mice [15]. These findings underscore the promising role of polysaccharides in addressing organ failure related to dysbiosis-induced inflammation.

Despite its promise as a strategy to improve the health of agricultural workers in Indonesia, a substantial research gap exists regarding the use of polysaccharides to prevent organ damage caused by pesticide-induced toxicity. While polysaccharides have shown potential in alleviating dysbiosis, the overall impact of polysaccharides on reducing oxidative stress and organ damage in vivo remains insufficiently explored. To the best of the authors' knowledge, the present study is the first systematic review and meta-analysis addressing this topic. Therefore, the aim of this study was to investigate the comprehensive effects of polysaccharides in mitigating pesticide toxicity in animal studies, focusing on biomarkers related to oxidative stress, antioxidant activity, kidney injury, lipid profiles, liver function, and the preservation of liver and kidney weights.

Methods

Study design and setting

The present systematic review and meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16]. A literature search was conducted from August 27th to September 10th, 2023, across multiple databases, including PubMed, Cochrane CENTRAL, Taylor & Francis, ScienceDirect, Scopus, Sage, ProQuest, EBSCOhost, and Google Scholar. Rayyan.ai was used to screen in vivo studies that met the predefined inclusion and exclusion criteria. The quality of the selected in vivo studies was evaluated using SYRCLE's Risk of Bias tool, specifically designed for in vivo studies. Data from the selected studies were extracted into a characteristics table and an outcome table for analysis. The independent variable was polysaccharides, and the dependent variables included: oxidative stress markers, measured by malondialdehyde (MDA) and nitric oxide (NO); antioxidant levels, measured by catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione (GSH); kidney injury biomarkers, measured by serum creatinine and urea; lipid profiles, measured by triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC); liver biomarkers, measured by aspartate aminotransferase

(AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP); and liver and kidney weights.

Eligibility criteria

Inclusion criteria were designed using the population, intervention, comparison, outcome, and study design (PICOS) framework. The population consisted of rats or mice exposed to pesticides, and the intervention involved administering polysaccharides, with a placebo serving as the comparison. The outcomes measured included oxidative stress markers, such as MDA and NO, as well as antioxidant levels, including CAT, SOD, GPx, and GSH. Kidney injury biomarkers, specifically serum creatinine and urea, were assessed, alongside lipid profiles comprising TG, HDL, LDL, and TC. Liver biomarkers, including AST, ALT, and ALP, were also analyzed. Additionally, liver and kidney weights were measured. The study design employed an in vivo experimental design. Exclusion criteria were as follows: (1) Studies comparing polysaccharides with other polysaccharides; (2) Studies published in languages other than English; (3) Studies reporting irrelevant outcomes; and (4) Studies with insufficient data for extraction, including study protocols or review articles.

Search strategy

The literature search was conducted from August 27 to September 10, 2023, using the following databases: PubMed, Cochrane CENTRAL, Taylor & Francis, ScienceDirect, Scopus, Sage, ProQuest, EBSCOhost, and Google Scholar. Search terms were developed in accordance with the Medical Subject Headings (MeSH) browser and combined using Boolean operators. The keywords used included: ("polysaccharide" OR "glycan") AND (("organophosphorus pesticide" OR "organophosphorus insecticide" OR "OPs" OR "organophosphate")) AND ("rat" OR "mice" OR "mouse" OR "BALB/c" OR "in vivo") (**Table 1**).

Table 1. Combined keywords employed in each database

Database	Keywords
PubMed	("polysaccharide"[MeSH Terms] OR (polysaccharide[Title/Abstract]) OR (glycan[Title/Abstract])) AND ("organophosphates"[MeSH Terms] OR (organophosphate[Title/Abstract]) OR (organophosphorus pesticide[Title/Abstract])) OR (organophosphorus insecticide[Title/Abstract])) OR (OPs[Title/Abstract])) AND ("Pediatrics"[MeSH Terms] OR ("mouse"[Title/Abstract] OR (mouse[Title/Abstract]) OR (rat[Title/Abstract])) OR (mice[Title/Abstract])) OR (BALB/C[Title/Abstract])) OR (in vivo[Title/Abstract]))
Cochrane Library	MeSH descriptor: [Polysaccharides] OR (polysaccharides):ti,ab,kw OR (glycans):ti,ab,kw AND MeSH descriptor: [Organophosphates] OR (organophosphate):ti,ab,kw OR (organophosphorus pesticide):ti,ab,kw OR (organophosphorus insecticide):ti,ab,kw OR (OPS):ti,ab,kw AND MeSH descriptor: [Mouse] OR (mouse):ti,ab,kw OR (rat):ti,ab,kw OR (mice):ti,ab,kw OR (BALB/C):ti,ab,kw
Google Scholar	("polysaccharide" OR "glycan") AND (“organophosphorus pesticide” OR "organophosphate") AND ("rat" OR "Mice" OR "Mouse" OR "In vivo")
Scopus	("polysaccharide" OR "glycan") AND ((“organophosphorus pesticide”) OR (“organophosphorus insecticide”) OR (“OPs”) OR ("organophosphate")) AND ("rat" OR "Mice" OR "Mouse" OR "BALB/C" OR "In vivo") Filter: Article
EbscoHOST	("polysaccharide" OR "glycan") AND ((“organophosphorus pesticide”) OR (“organophosphorus insecticide”) OR (“OPs”) OR ("organophosphate")) AND ("rat" OR "Mice" OR "Mouse" OR "BALB/C" OR "In vivo")
Taylor and Francis	("polysaccharide" OR "glycan") AND ((“organophosphorus pesticide”) OR (“organophosphorus insecticide”) OR (“OPs”) OR ("organophosphate")) AND ("rat" OR "Mice" OR "Mouse" OR "BALB/C" OR "In vivo")
ScienceDirect	("polysaccharide" OR "glycan") AND (“organophosphorus pesticide” OR "organophosphate") AND ("rat" OR "Mice" OR "Mouse" OR "In vivo") Filter: Research article
Sage	("polysaccharide" OR "glycan") AND (“organophosphorus pesticide” OR "organophosphate") AND ("rat" OR "Mice" OR "Mouse" OR "In vivo")
Proquest	("polysaccharide" OR "glycan") AND ((“organophosphorus pesticide”) OR (“organophosphorus insecticide”) OR (“OPs”) OR ("organophosphate")) AND ("rat" OR "Mice" OR "Mouse" OR "BALB/C" OR "In vivo") Filter: Article

Data selection and screening

All relevant studies retrieved from the databases were compiled using Rayyan.ai (Rayyan Systems Inc., Doha, Qatar). Three independent reviewers (S.A.A., S.S.F., D.E.P.) screened the titles and abstracts of the selected studies after duplicates were removed. A fourth reviewer (E.N.S.) served as the final decision-maker in cases of disagreements through joint discussion. All search results were entered into Rayyan.ai to check for duplicates, which were then removed. Articles that did not meet the automatic exclusion criteria were further screened based on the inclusion criteria, and full-text versions were assessed for eligibility.

Data extraction

The data extracted from the selected studies included the author, year of publication, country, sample size, rat type, polysaccharide and pesticide types and dosages, experimental design, duration, and adverse events. The outcomes measured included oxidative stress markers, such as MDA and NO, as well as antioxidant levels, including CAT, SOD, GPx, and GSH. Kidney injury biomarkers, specifically serum creatinine and urea, were assessed, alongside lipid profiles comprising TG, HDL, LDL, and TC. Liver biomarkers, including AST, ALT, and ALP, were also analyzed. Additionally, liver and kidney weights were measured.

Quality assessment

The quality of the included studies was assessed using SYRCLE's Risk of Bias (RoB) tool [16], covering ten domains, including selection, performance, detection, attrition, and reporting bias. Each domain was evaluated as "low risk," "high risk," or "unclear risk" based on signaling questions. A study's overall risk of bias was determined by the ratings across all domains. Studies with multiple "high risk" ratings were considered unreliable, while those with mostly "low risk" were deemed more reliable. Three independent reviewers (S.A.A., S.S.F., D.E.P.) conducted the assessment, with a fourth reviewer (E.N.S.) resolving disagreements. Outcomes were documented in the Bias domain file and uploaded to Review Manager 5.4.1 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) for summary and traffic light display.

Statistical analysis

Statistical analysis was performed using Review Manager 5.4.1. A random-effects meta-analysis was employed to combine individual study data, accounting for clinical and methodological diversity. Outcomes were synthesized using mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI). MD was used for studies measuring the same outcome with the same units, while SMD was used for studies measuring the same outcome with different scales. If heterogeneity was low, a fixed-effect model was used. The I^2 statistic was calculated to assess heterogeneity, with values ranging from 0% to 100%, where an I^2 value greater than 50% indicates moderate to high heterogeneity. Polysaccharide doses were categorized for meta-analysis as follows: ≤25 mg/kg BW, ≥45 mg/kg BW, 26–50 mg/kg BW, ≥50 mg/kg BW, 51–100 mg/kg BW, ≥100 mg/kg BW, 101–200 mg/kg BW, <150 mg/kg BW, >150 mg/kg BW, >200 mg/kg BW, 150–180 mg/kg BW, 201–300 mg/kg BW, and >300 mg/kg BW.

Results

Article selection process

The article selection process involved multiple stages: identification, screening, and inclusion. During the identification stage, 246 duplicate articles were removed, leaving 1,683 articles for further review. In the screening phase, 1,616 articles were automatically excluded by Rayyan.ai according to the PICOS framework, resulting in 67 articles for further evaluation. Following the review of titles and abstracts, 2 articles were excluded, leaving 65 articles for detailed assessment. Subsequently, 5 studies were excluded for comparing other polysaccharides, 12 due to language incompatibility, 18 for reporting irrelevant outcomes, and 17 for insufficient data. Ultimately, 13 studies were included in systematic review and meta-analysis (**Figure 1**).

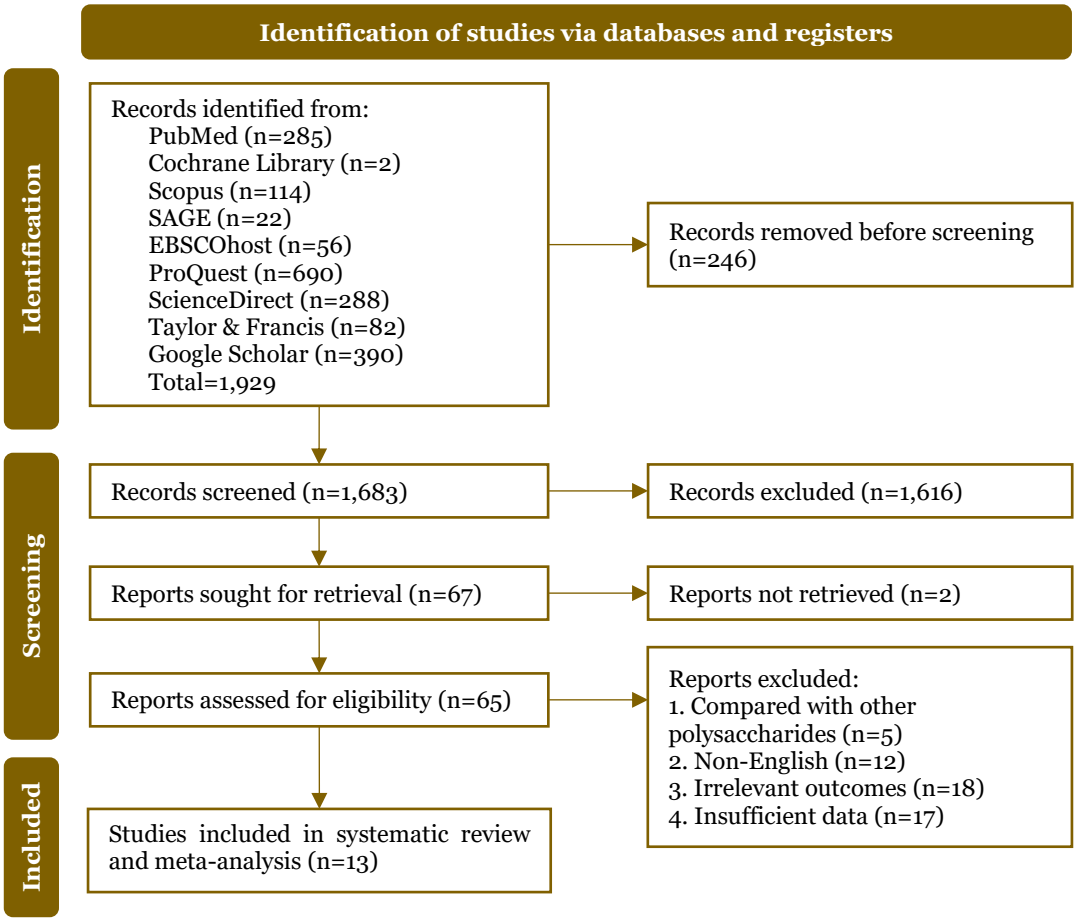

Figure 1. PRISMA flow diagram depicting the article selection process.

A total of 367 samples were included, comprising 238 rats/mice in the intervention group and 129 in the control group. The studies were conducted across various countries: Egypt (n=5), China (n=3), India (n=2), Saudi Arabia (n=2), Serbia (n=1), and the Slovak Republic and Poland (n=1). The included studies used various strains of rats and mice: male Wistar albino rats (*Rattus norvegicus*), male Sprague-Dawley rats (*Rattus norvegicus*), male Kunming mice (*Mus musculus*), female CD-1 ICR mice (strain CD-1 from Institute of Cancer Research; *Mus musculus*), and male albino mice (*Mus musculus*) (**Table 2**).

The polysaccharides used in the included studies varied in type and dosage. Fucoidan was administered at doses of 100 and 200 mg/kg BW. Wheat germ oil was used at 400 mg/kg BW, while Flaxseed was provided as a 10% supplement to the basal diet, with the Libra variety containing 57% alpha-linolenic acid content. *Viscum album L. leaf extract* was given at lower and higher doses of 175 mg/kg BW and 350 mg/kg BW, respectively. *Quillaja saponaria* was administered as 30% of the basal diet. Okra polysaccharides were used at 5 mL/kg BW, and sodium aescinate was administered at doses of 0.45, 0.9, and 1.8 mg/kg BW. *Aloe vera* leaf aqueous extract was provided at 420 mg/kg BW, while red algae was given at 200 mg/kg BW. Pectin was administered at doses of 50 and 25 mg/kg BW, and *Nigella sativa* oil was used at 4 mL/kg BW. Lastly, pea polysaccharides were used at concentrations of 100 mg/L, 200 mg/L, and 300 mg/L (**Table 2**).

The pesticides used in the included studies were as follows: diazinon was administered at 20 mg/kg BW, while malathion was used at 100 mg/kg BW. Xylene was provided at 400 mg/kg BW per day, and chlorpyrifos was given at 35 mg/kg BW. Chlorfenapyr was administered at 180 mg/kg BW, and a 1.2 mL/kg BW mixture of 0.8% carbon tetrachloride in peanut oil was used. Methyl parathion was given as a single dose of 15 mg/kg BW intragastrically. The combination of cartap and malathion was used at 29 mg/kg BW. Imidacloprid was provided at 45 mg/kg BW (high dose) and 22.5 mg/kg BW (low dose). Octylphenol was administered at 50 mg/kg BW, and glyphosate was used at 90 mg/L (**Table 2**). Furthermore, no adverse events were reported in the studies included in the present systematic review.

Table 2. Characteristics of the included studies

Author, year	Country	Sample size (n)		Type of rats	Polysaccharide (Type; Dose)	Pesticide (Type; Dose)	Experimental design	Duration (weeks)
		I	C					
Du *et al.*, 2011 [17]	China	32	8	Male Sprague-Dawley rats (*Rattus norvegicus)*	SA: 0.45 mg/kg BW, 0.9 mg/kg BW, 1.8 mg/kg BW	MP: Single dose of 15 mg/kg BW intragastrically	- MP + SA group: Received intragastric MP at a dose of 15 mg/kg BW to induce acute MP intoxication, following SA via the tail vein 2.5 hours post-MP administration - Control group: Received normal saline in corresponding volumes	N/A
Koriem *et al.*, 2014 [18]	Egypt	16	8	Male Wistar Albino rats (*Rattus norvegicus)*	Pectin: 50 mg/kg BW, 25 mg/kg BW	OP: 50 mg/kg BW	- OP group: Received 50 mg/kg BW OP via i.p. for 3 days/week - OP + Pectin 1 group: Received 50 mg/kg BW OP + 25 mg/kg BW pectin via i.p. for 3 days/week - OP + Pectin 2 group: Received 50 mg/kg BW OP + 50 mg/kg BW pectin via i.p. for 3 days/week	3
Zhao *et al.*, 2016 [19]	China	10	5	Male Kunming mice (*Rattus norvegicus)*	TPs: 100 mg/L, 200 mg/L, 300 mg/L	GLY: 90 mg/L	Three experimental groups were pretreated with TPs (100, 200, and 300 mg/L) for 24 hours, followed by 90 mg/L of GLY for 24 hours - Group GLY: 90 mg/L GLY - TPs1+GLY: 100 mg/L TPs + 90 mg/L GLY - TPs2+GLY: 200 mg/L TPs + 90 mg/L GLY - TPs3+GLY: 300 mg/L TPs + 90 mg/L GLY	24 hours
Reda *et al.*, 2018 [20]	Egypt	5	5	Male Albino mice (*Mus musculus)*	*Nigella sativa* oil: 4 mL/kg BW	IMI: 2.6 mg/kg BW	- IMI group: Received 2.6 mg/kg BW IMI - IMI + NS oil group: Received 2.6 mg/kg BW IMI + 4 mL/kg BW NS oil	4
Gupta *et al.*, 2019 [21]	India	42	6	Male Wistar albino rats (*Rattus norvegicus)*	*Aloe vera* leaf aqueous extract: 420 mg/kg BW	Cartap and malathion: 29 mg/kg BW	- Control group: Had unrestricted access to feed and water - *Aloe vera* extract group: Received 420 mg/kg BW of *Aloe vera* extract - Cartap-treated group: Received 10% of the LD50 (29 mg/kg BW) of cartap - Malathion-treated group: Received 10% of the LD50 (29 mg/kg BW) of malathion - Combined cartap and malathion group: Received a mixture of 5% LD50 (14.5 mg/kg BW) cartap and 5% LD50 (14.5 mg/kg BW) malathion - *Aloe vera* + Cartap group: Received *Aloe vera* (420 mg/kg BW) followed by cartap at 10% LD50 (29 mg/kg BW) - Aloe vera + Malathion group: Received *Aloe vera* (420 mg/kg BW) followed by malathion at 10% LD50 (29 mg/kg BW) - *Aloe vera* + Cartap + Malathion group: Received Aloe vera (420 mg/kg BW) followed by a mixture of 5% LD50 (14.5 mg/kg BW) cartap and 5% LD50 (14.5 mg/kg BW) malathion	2
Abdel-Daim *et al.*, 2020 [22]	Egypt and Saudi Arabia	16	8	Male Wistar albino rats (*Rattus norvegicus)*	FUC: 100 and 200 mg/kg BW	DZN: 20 mg/kg BW	- FUC group: Administered FUC orally at doses of 100 mg/kg BW and 200 mg/kg BW daily - Control group: Received diazinon via subcutaneous injection at a dose of 20 mg/kg BW daily	4

Author, year	Country	Sample size (n)		Type of rats	Polysaccharide (Type; Dose)	Pesticide (Type; Dose)	Experimental design	Duration (weeks)
		I	C					
Andrejcáková *et al.*, 2021 [23]	Slovak Republic and Poland	20	20	Female CD-1 ICR Mice (*Mus musculus)*	Flaxseed: 10% supplement to basal diet; variety Libra; 57% content of ALA	Xylene: 400 mg/kg BW/day	- Flaxseed group: Received flaxseed (10%; variety Libra; containing 57% ALA) - Control group: Received xylene (mixed xylene p.a., diluted 1:10 in water) at 10 mL per head daily, equivalent to 400 mg/kg BW/day, via cannula	2
Reda *et al.*, 2021 [24]	Egypt	15	5	Male Wistar Albino rats (*Rattus norvegicus)*	QS: 30% of basal diet	CFp: 180 mg/kg BW	- Control group: Provided with a commercial basal diet - QS group: Received QS at 30% of the basal diet - CFp group: Administered CFp at a dosage of 180 mg/kg BW - CFp + QS group: Received CFp (180 mg/kg BW) and QS (30% of basal diet)	4
Hossam *et al.*, 2022 [25]	Egypt	10	10	Male Wister Albino rats (*Rattus norvegicus)*	Red algae: 200 mg/kg BW	IMI: 45 mg/kg BW (high dose), 22.5 mg/kg BW (low dose)	Dissolved IMI in corn oil was administered by oral gavage daily for 28 days, with a 200 mg/kg red algae pretreatment in distilled water, given 30 minutes prior for antioxidant protection - Group 1: IMI 45 mg/kg BW (1/10 LD50, high dose) - Group 2: IMI 22.5 mg/kg BW (1/20 LD50, low dose) - Group 3: Red algae 200 mg/kg BW + high dose IMI - Group 4: Red algae 200 mg/kg BW + low dose IMI	4
Gupta *et al.*, 2023 [26]	India	18	6	Male Wistar albino rats (*Rattus norvegicus)*	*Aloe vera* leaf aqueous extract: 420 mg/kg BW	Malathion: 29 mg/kg BW	- Control group: Had unrestricted access to feed and water - *Aloe vera* extract group: Received 420 mg/kg BW of *Aloe vera* extract - Malathion-treated group: Received 10% of the LD50 (29 mg/kg BW) of malathion - Aloe vera + Malathion group: Received *Aloe vera* (420 mg/kg BW) followed by malathion at 10% LD50 (29 mg/kg BW)	2
Miloševic *et al.*, 2023 [27]	Serbia	12	6	Male Wistar Albino rats (*Rattus norvegicus)*	VAE: 175 mg/kg BW (lower dose); 350 mg/kg BW (higher dose)	CPF: 35 mg/kg BW	- VAE group: Received VAE at doses of 175 mg/kg BW (lower dose) and 350 mg/kg BW (higher dose) - Control group: Received CPF at 35 mg/kg BW, with treatments administered twice per week	4
Yan *et al.*, 2023 [28]	China	30	30	Male Kunming mice (*Mus musculus)*	OPS: 5 mL/kg BW	1.2 mL/kg BW of 0.8% (v/v) CCl4/peanut oil mixture	All mice received intragastric administration at a dosage of 5 mL/kg BW for 28 consecutive days - Intervention group: Received an intraperitoneal injection of a 0.8% (v/v) CCl4/peanut oil mixture (1.2 mL/kg BW) - Control group: Treated with 1.2 mL/kg BW of peanut oil via intraperitoneal injection	4
Alkhalaf *et al.*, 2024 [29]	Saudi Arabia	12	12	Male Wistar albino rats (*Rattus norvegicus)*	WGO: 400 mg/kg BW	MAL: 100 mg/kg BW	- WGO group: Received WGO (400 mg/kg BW) with the basal diet following MAL induction - Control group: Received MAL at a dose of 100 mg/kg BW with the basal diet	4

C: Control; CCl4: carbon tetrachloride; CD-1 ICR: CD-1 strain mice from Institute of Cancer Research; CFp: chlorfenapyr; CPF: chlorpyrifos; DZN: diazinon; FUC: fucoidan from *Laminaria japonicum*; GLY: glyphosate; I: intervention; IMI: imidacloprid; MAL: malathion; MP: methyl parathion; N/A: not available; OP: octyl phenol; OPS: okra polysaccharides; QS: quinoa seed; SA: sodium aescinate; TPs: tea polysaccharides; VAE: *Viscum album* L. leaf extract; WGO: wheat germ oil

The pesticides used in the included studies were as follows: diazinon was administered at 20 mg/kg BW, while malathion was used at 100 mg/kg BW. Xylene was provided at 400 mg/kg BW per day, and chlorpyrifos was given at 35 mg/kg BW. Chlorfenapyr was administered at 180 mg/kg BW, and a 1.2 mL/kg BW mixture of 0.8% carbon tetrachloride in peanut oil was used. Methyl parathion was given as a single dose of 15 mg/kg BW intragastrically. The combination of cartap and malathion was used at 29 mg/kg BW. Imidacloprid was provided at 45 mg/kg BW (high dose) and 22.5 mg/kg BW (low dose). Octylphenol was administered at 50 mg/kg BW, and glyphosate was used at 90 mg/L (**Table 2**). Furthermore, no adverse events were reported in the studies included in the present systematic review.

Risk of bias

A total of nine studies demonstrated a high overall risk of bias, primarily due to issues with blinding of both the intervention and outcome assessment [17-21,23,27-29]. Additionally, several other studies showed some concerns regarding bias [22,24-26]. Specifically, 46% of the studies exhibited an unclear risk of bias regarding random sequence generation and allocation concealment, 7.6% showed unclear selection bias in baseline characteristics, and 7.6% demonstrated a high risk of bias in other areas [23]. All studies (100%) showed a low risk of bias in incomplete outcome data and selective reporting. For studies with a high risk of bias, corrective actions were taken to address these issues, rather than excluding them, suggesting that the results might differ from those with low bias (**Figure 2**).

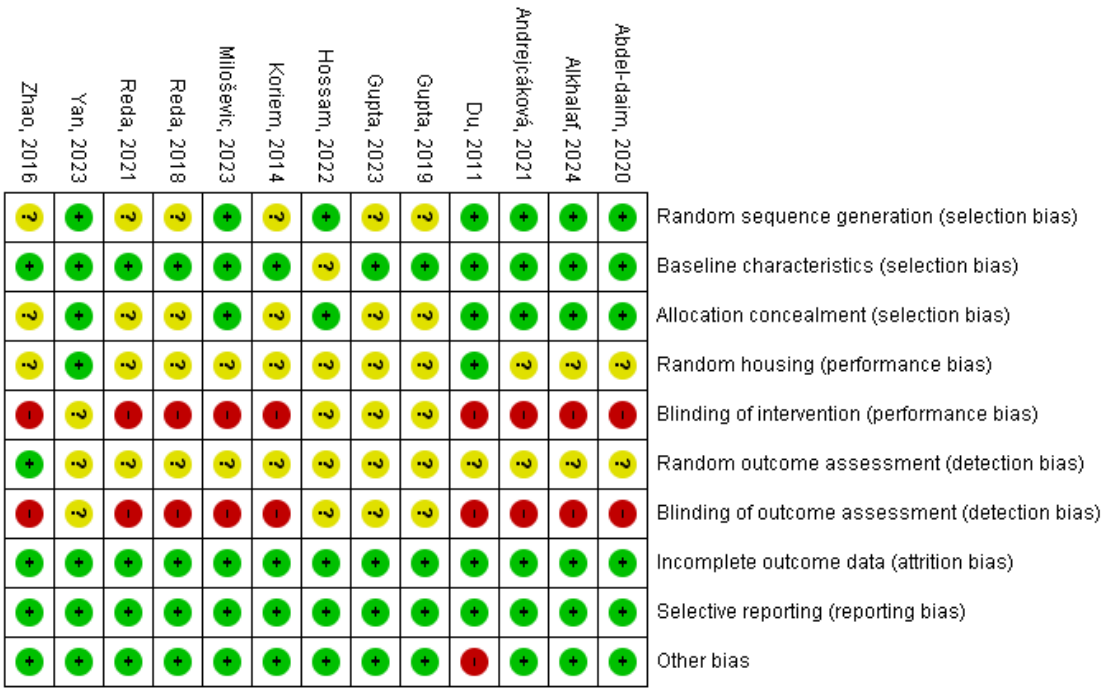

Figure 2. Risk of bias assessment using the SYRCLE Risk of Bias tool.

Effects of polysaccharides on oxidative stress in pesticide-exposed animal models

Malondialdehyde levels

Six studies assessed the effects of polysaccharides (quinoa seeds, Aloe vera leaf, red algae, pectin, and tea polysaccharides) on MDA levels, with doses ranging from ≤25 mg/kg BW to >300 mg/kg BW [18,19,21,24-26]. Significant differences in MDA levels were observed across all dose ranges: ≤25 mg/kg BW (p=0.02), 26–50 mg/kg BW (p=0.0009), 51–100 mg/kg BW (p=0.001), 101–200 mg/kg BW (p<0.0001), 201–300 mg/kg BW (p=0.0008), and >300 mg/kg BW (p=0.008). The overall effect size revealed a statistically significant reduction in MDA levels (Pooled SMD: -3.28; 95%CI: -4.40–[-2.15]; p<0.00001), with high heterogeneity among studies (I^2=67%; Tau^2=1.96; Chi^2=27.63; p-heterogeneity=0.001) (**Figure 3**). These findings suggest that polysaccharides significantly reduce MDA levels in pesticide-exposed animal models.

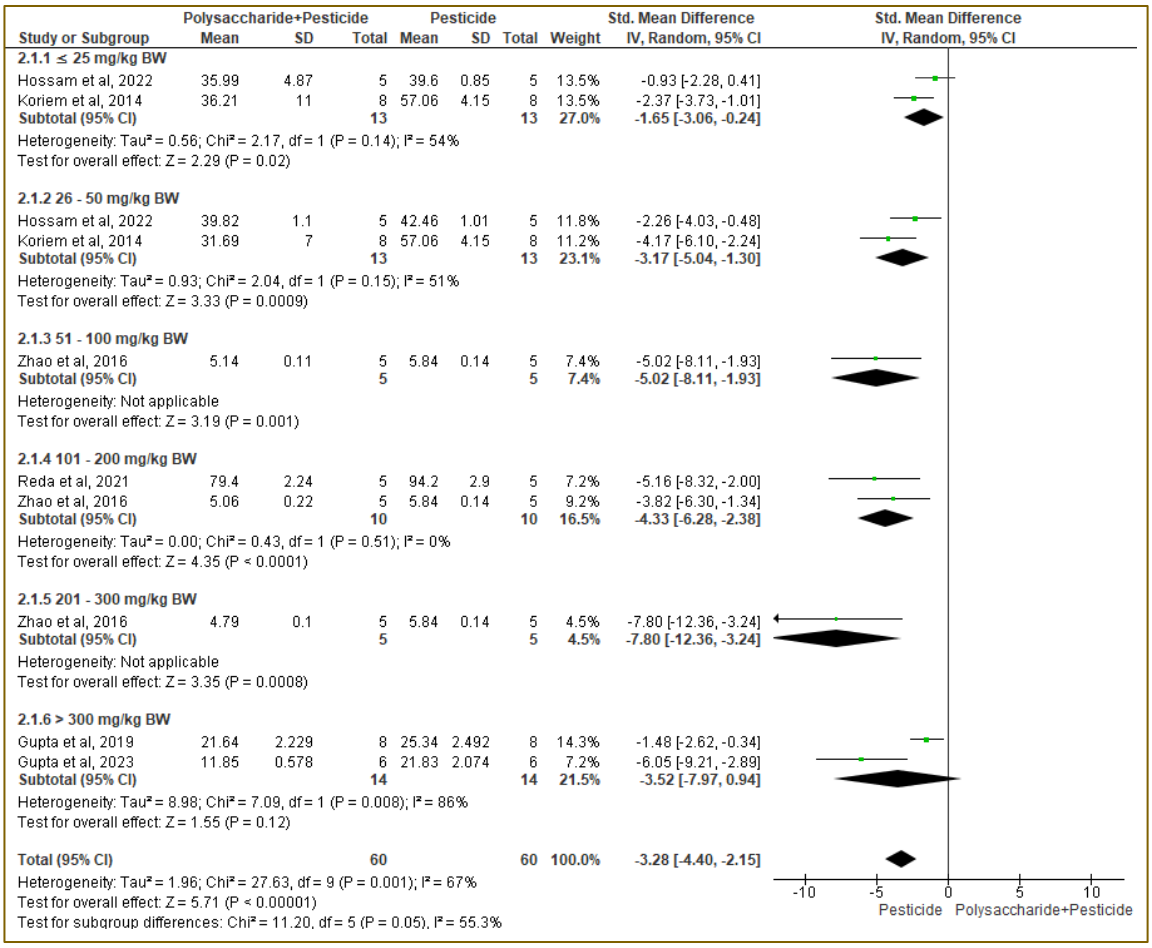

Figure 3. Forest plot of the meta-analysis on malondialdehyde (MDA) levels, comparing the effects of various polysaccharide doses (≤25 mg/kg BW, 26–50 mg/kg BW, 51–100 mg/kg BW, 101–200 mg/kg BW, 201–300 mg/kg BW, and >300 mg/kg BW) to pesticide-only exposure.

Nitric oxide levels

Two studies evaluated the effects of polysaccharides (sodium aescinate and pectin) on NO levels in pesticide-exposed animal models [23,27]. The polysaccharide doses ranged from 0.45 mg/Kg BW to 50 mg/Kg BW. The overall effect size showed a statistically significant reduction in NO levels (Pooled MD: -5.23; 95%CI: -7.86–[-2.61]; p<0.0001), indicating a meaningful effect of the intervention. No heterogeneity was observed among the studies (I^2=0%; Chi²=0.07; p-heterogeneity=0.79), suggesting that the results are consistent across studies. These findings suggest that polysaccharides significantly reduce NO levels in pesticide-exposed animal models with consistent effects (**Figure 4**).

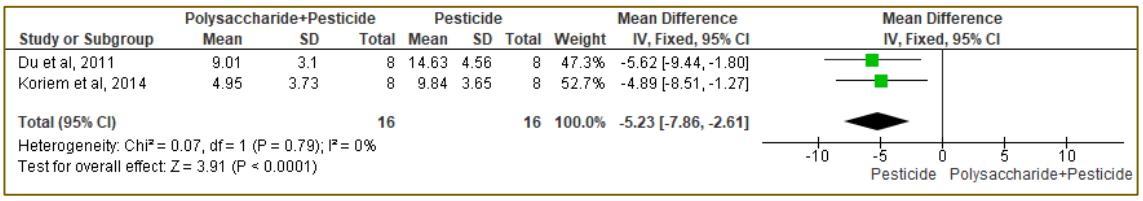

Figure 4. Forest plot of the meta-analysis on nitric oxide (NO) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

Effects of polysaccharides on antioxidant markers in pesticide-exposed animal models

Catalase levels

Two studies investigated the effects of various polysaccharides (red algae and pectin) on CAT levels in pesticide-exposed animal models, with doses ranging from ≤25 mg/kg BW to >45 mg/kg

BW [26,27]. Significant differences in CAT levels were observed across all polysaccharide dose ranges, including ≤25 mg/kg BW (p<0.00001) and ≥45 mg/kg BW (p<0.0001). The overall effect size revealed a statistically significant effect on CAT levels (Pooled MD: 1.84; 95%CI: 1.50–2.18; p=0.00001). Additionally, no heterogeneity was observed among studies (I^2=0%; Chi²=0.12; p-heterogeneity=0.99), indicating consistent results across studies. These findings suggest that polysaccharides significantly elevate CAT levels in response to pesticide exposure, demonstrating a consistent effect with no variation across studies (**Figure 5**).

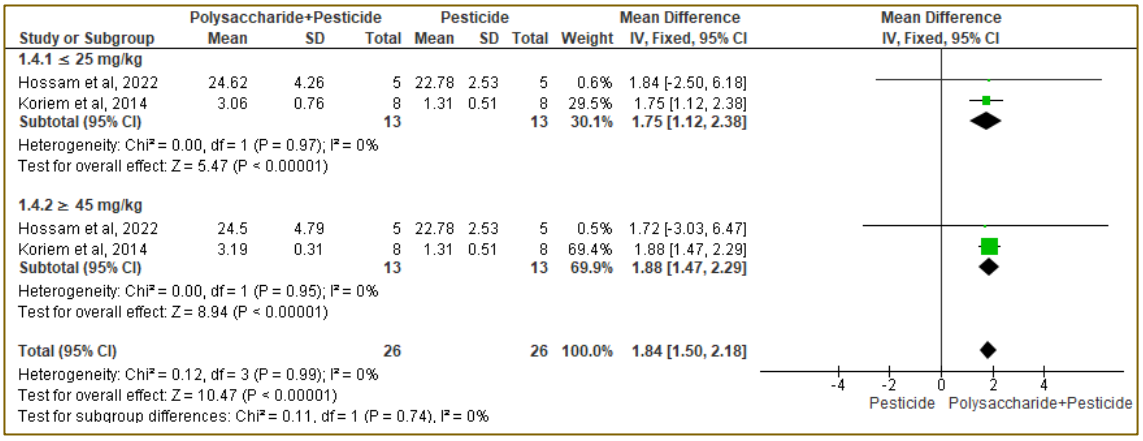

Figure 5. Forest plot of meta-analysis assessing catalase (CAT) levels, comparing the effect of various polysaccharide doses (≤25 mg/kg BW to >45 mg/kg BW) to pesticide-only exposure.

Superoxide dismutase levels

Four studies evaluated the effects of polysaccharides (quinoa seeds, red algae, pectin, tea polysaccharides) on SOD levels in pesticide-exposed animal models, with doses ranging from ≤25 mg/kg BW to 300 mg/kg BW [21,26,27,29]. Significant differences in SOD levels were observed with polysaccharide doses of ≤25 mg/kg BW (p<0.00001), 51–100 mg/kg BW (p=0.04), and 201–300 mg/kg BW (p=0.0008). No significant differences were found for doses of 26–50 mg/kg BW (p=0.14) and 101–200 mg/kg BW (p=0.24). The overall effect size revealed a statistically significant impact on SOD levels (Pooled SMD: 3.77; 95%CI: 2.07–5.48; p<0.0001), indicating that polysaccharides significantly increase SOD levels. However, high heterogeneity (I^2=79%; Tau²=4.31; Chi²=34.07; p-heterogeneity<0.0001) indicates that varying polysaccharide doses likely influenced the results, with considerable true variability and significant differences among study outcomes. Overall, polysaccharides significantly enhance SOD levels in response to pesticide exposure, with consistent effects observed, although variability exists across studies (**Figure 6**).

Glutathione peroxidase levels

Two studies evaluated the effects of polysaccharides (red algae and pectin) on GPx levels in pesticide-exposed animal models, using doses ranging from ≤25 mg/kg BW to ≥45 mg/kg BW [26,27]. Significant differences in GPx levels were observed across all polysaccharide dose ranges, with doses ≤25 mg/kg BW (p=0.001) and ≥45 mg/kg BW (p<0.0001) showing significant effects. The overall effect size revealed statistically significant effects on GPx levels (Pooled SMD: 1.90; 95%CI: 1.19–2.61; p<0.00001), suggesting a meaningful intervention effect. With very low heterogeneity among studies (I^2=9%; Chi²=3.28; p-heterogeneity=0.35), there is strong evidence of homogeneity, indicating minimal variability in study outcomes. These findings suggest that polysaccharides significantly elevate GPx levels in pesticide-exposed animal models (**Figure 7**).

Glutathione levels

Five studies evaluated the effect of polysaccharides (quinoa seeds, *Aloe vera* leaf, red algae, pectin) on GSH levels in pesticide-exposed animal models, with polysaccharide doses ranging from ≤25 mg/kg BW to >50 mg/kg BW [21,24-27]. Significant differences in GSH levels were observed at doses of ≤25 mg/kg BW (p=0.003) and >50 mg/kg BW (p=0.05), but no significant differences were found at doses of 26–50 mg/kg BW (p=0.0001). The overall effect analysis

revealed a statistically significant effect on GSH levels (Pooled SMD: 2.61; 95%CI: 1.35–3.86; p<0.0001). Moderate to high heterogeneity was observed among studies (I^2=74%; Tau²=2.00; Chi²=22.69; p-heterogeneity=0.0009), indicating that factors such as varying polysaccharide doses likely influenced the results. The Tau² value suggests moderate true variability, while the Chi² value supports significant differences among study outcomes. These findings suggest that polysaccharides significantly enhance GSH levels in pesticide-exposed animal models (**Figure 8**).

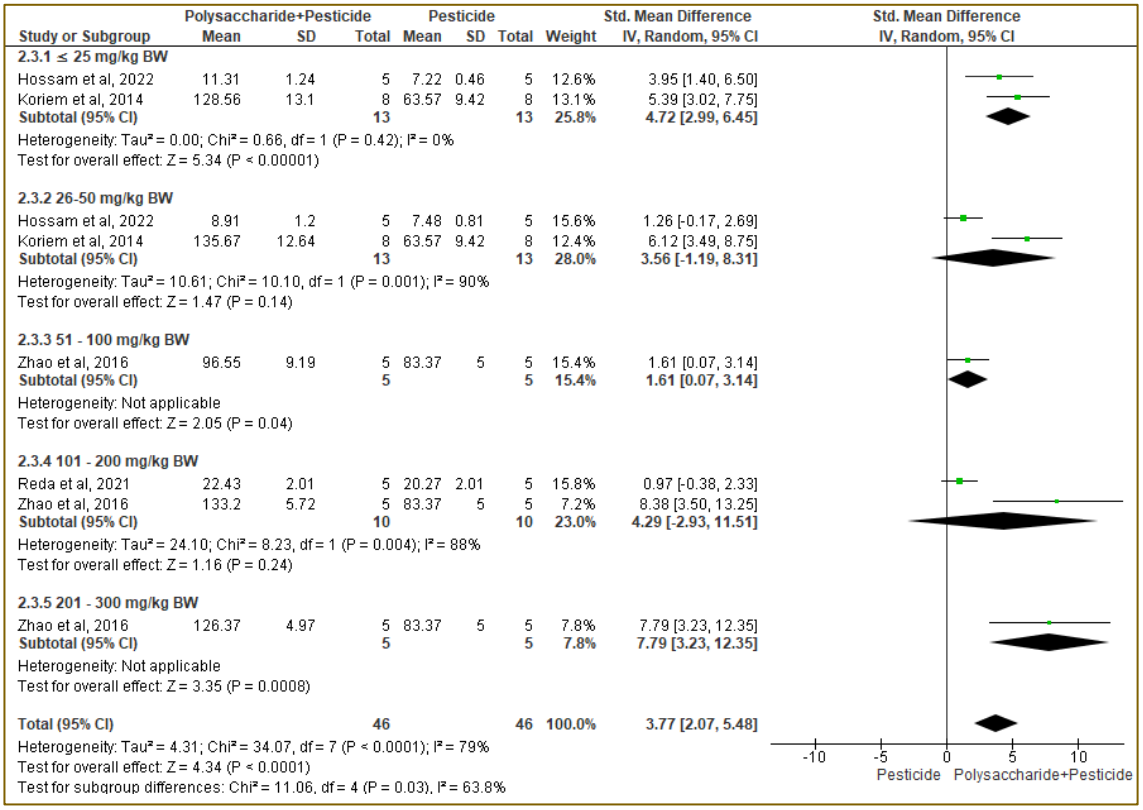

Figure 6. Forest plot of meta-analysis assessing superoxide dismutase (SOD) levels, comparing the effects of various polysaccharide doses (≤25 mg/kg body weight [BW], 26–50 mg/kg BW, 51–100 mg/kg BW, 101–200 mg/kg BW, and 201–300 mg/kg BW) to pesticide-only exposure.

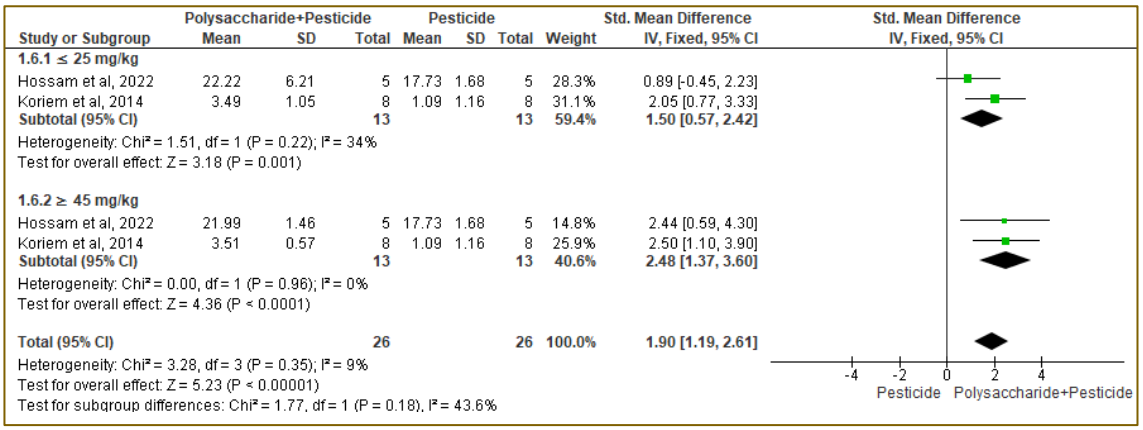

Figure 7. Forest plot of meta-analysis assessing glutathione peroxidase (GPx) levels, comparing the effects of various polysaccharide doses (≤25 mg/kg BW to ≥45 mg/kg BW) to pesticide-only exposure.

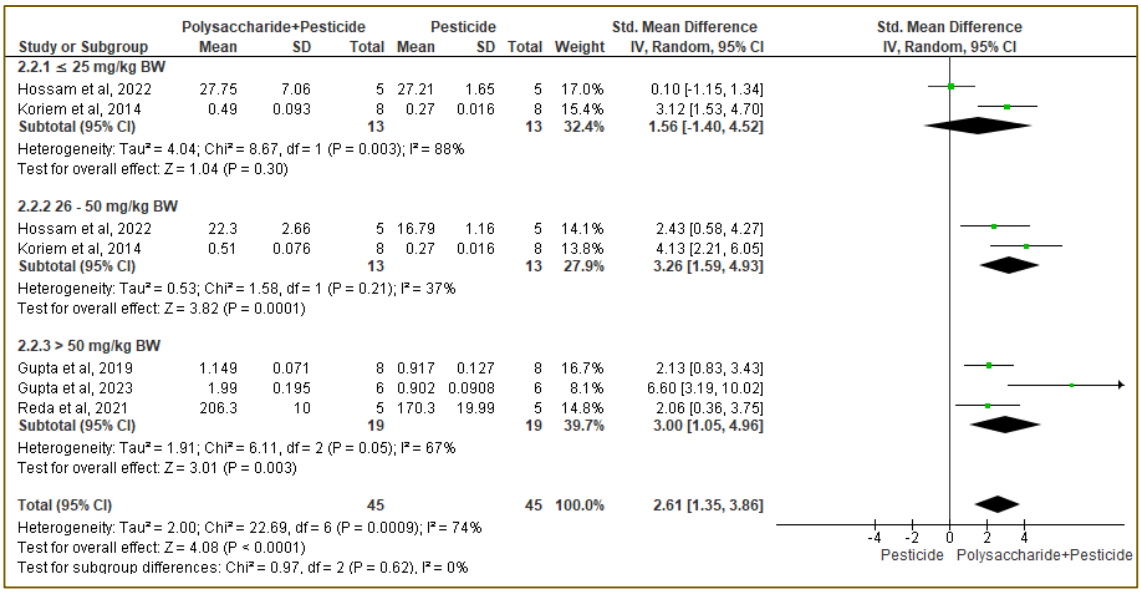

Figure 8. Forest plot of meta-analysis assessing glutathione (GSH) levels, comparing the effects of various polysaccharide doses (≤25 mg/kg body weight [BW] to >50 mg/kg BW) to pesticide-only exposure.

Effects of polysaccharides on liver damage and functional performance in pesticide-exposed animal models

Alanine aminotransferase levels

Five studies assessed the effect of polysaccharides (fucoidan from *Laminaria japonicum*, wheat germ oil, flaxseed, *Viscum album* L. leaf extract, *Nigella sativa* oil) on ALT levels in pesticide-exposed animal models [17-20,28]. Polysaccharide supplementation significantly decreased ALT levels (Pooled SMD: -3.57; 95%CI: -6.06–[-1.08]; p=0.005). High heterogeneity was observed (I^2=90%; Tau²=5.76; Chi²=38.48; p-heterogeneity<0.00001), suggesting that factors beyond random variation, such as differing polysaccharide doses, likely influenced the results. Tau² value indicates moderate variability in ALT levels, while the Chi² value supports significant differences among study outcomes. These findings indicate that polysaccharides significantly reduce hepatic injury, as evidenced by decreased ALT levels, in pesticide-exposed animal models (**Figure 9**).

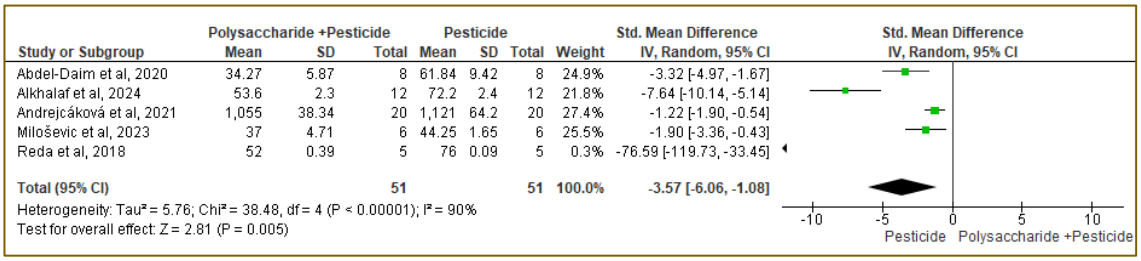

Figure 9. Forest plot of the meta-analysis on alanine aminotransferase (ALT) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

Aspartate aminotransferase levels

Five studies evaluated the effect of polysaccharides (fucoidan from *Laminaria japonicum*, wheat germ oil, flaxseed, *Viscum album* L. leaf extract, *Nigella sativa* oil) on AST levels in pesticide-exposed animal models [17–20,28]. Polysaccharide supplementation significantly decreased levels of AST (Pooled SMD: -4.77; 95%CI: -7.15–[-2.39]; p<0.0001). High heterogeneity was observed (I^2=80%; Tau²=4.89; Chi²=19.55; p-heterogeneity=0.0006), indicating that factors other than random variation, such as differing polysaccharide doses, likely influenced the results. Tau² value suggests moderate variability in AST levels across studies, while Chi² value supports significant differences among study outcomes. These findings indicate that polysaccharides significantly reduce hepatic injury as measured by decreased AST levels in pesticide-exposed animal models (**Figure 10**).

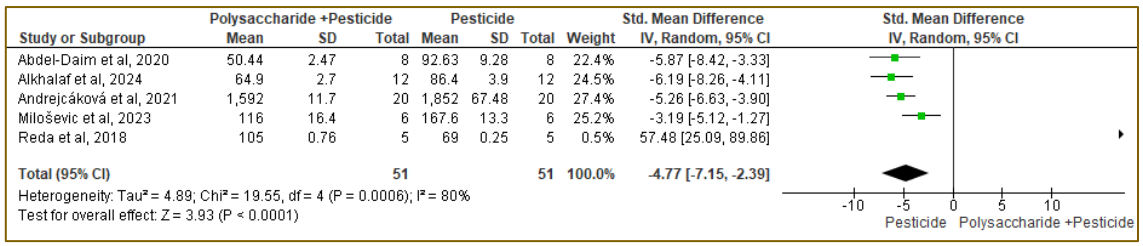

Figure 10. Forest plot of the meta-analysis on aspartate aminotransferase (AST) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

Alkaline phosphatase

Two studies evaluated the effect of polysaccharides (fucoidan from *Laminaria japonicum* 100 and 200 mg/kg BW; and wheat germ oil 400 mg/kg BW) on ALP levels in pesticide-exposed animal models [17,18]. Polysaccharide supplementation significantly reduced hepatic injury, as indicated by the decreased levels of ALP (Pooled SMD: -5.95; 95%CI: -7.55–[-4.34]; p<0.00001). Moderate heterogeneity was observed (I^2=50%; Chi²=2.00; p-heterogeneity=0.16), suggesting that factors other than random variation likely influenced the results, possibly due to the limited number of studies on this outcome. These findings indicate that polysaccharides significantly reduce hepatic injury, as reflected by ALP levels, in pesticide-exposed animal models (**Figure 11**).

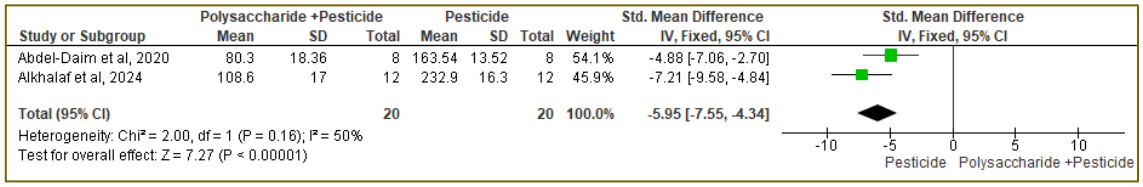

Figure 11. Forest plot of the meta-analysis on alkaline phosphatase (ALP) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

Liver weight

Four studies evaluated the effect of polysaccharides on liver weight in pesticide-exposed animal models, comparing polysaccharide (*Viscum album L.* leaf extract, quinoa seed, *Aloe vera* leaf aqueous extract and *Nigella sativa* oil) doses of <150 mg/kg BW, 150–180 mg/kg BW, and >180 mg/kg BW [20,21,24,28]. The overall analysis revealed that liver weight was significantly higher in the pesticide-only group compared to the intervention group (Pooled SMD: -0.7; 95%CI: -1.23–[-0.17]; p=0.009). No significant differences in liver weight were found for doses 150–180 mg/kg BW (p=0.11) and >180 mg/kg BW (p=0.002), but was not applicable for doses <150 mg/kg BW due to there being only one study representing this dose result. Very low heterogeneity (I²=0%; Tau²=0.00; Chi²=2.69; p-heterogeneity=0.61) was found for this outcome. These results indicate that polysaccharide supplementation significantly reduced liver weight in pesticide-exposed animal models compared to the pesticide-only group (**Figure 12**).

Effects of polysaccharides on kidney damage and functional performance in pesticide-exposed animal models

Creatinine levels

Two studies evaluated the effect of polysaccharides (fucoidan from *Laminaria japonicum* and *Nigella sativa* oil) on creatinine levels in pesticide-exposed animal models, with polysaccharide doses divided into <150 mg/kg BW and >150 mg/kg BW groups [17,28]. Significant differences in creatinine levels were observed for both dosing groups: <150 mg/kg BW (p<0.0001) and >150 mg/kg BW (p<0.00001). The overall effect size yielded a significant difference (Pooled MD: -1.29; 95%CI: -1.66–[-0.92]; p<0.00001), with high heterogeneity (I^2=82%; Tau²=0.08; Chi²=11.14; p-heterogeneity=0.004), suggesting factors beyond random variation, likely due to varying doses across studies. The Tau² value indicates low true variability, while the Chi² value supports

significant differences among study outcomes. These findings suggest that pesticide exposure increases the risk of renal damage, as elevated creatinine levels are a marker of impaired kidney function (**Figure 13**).

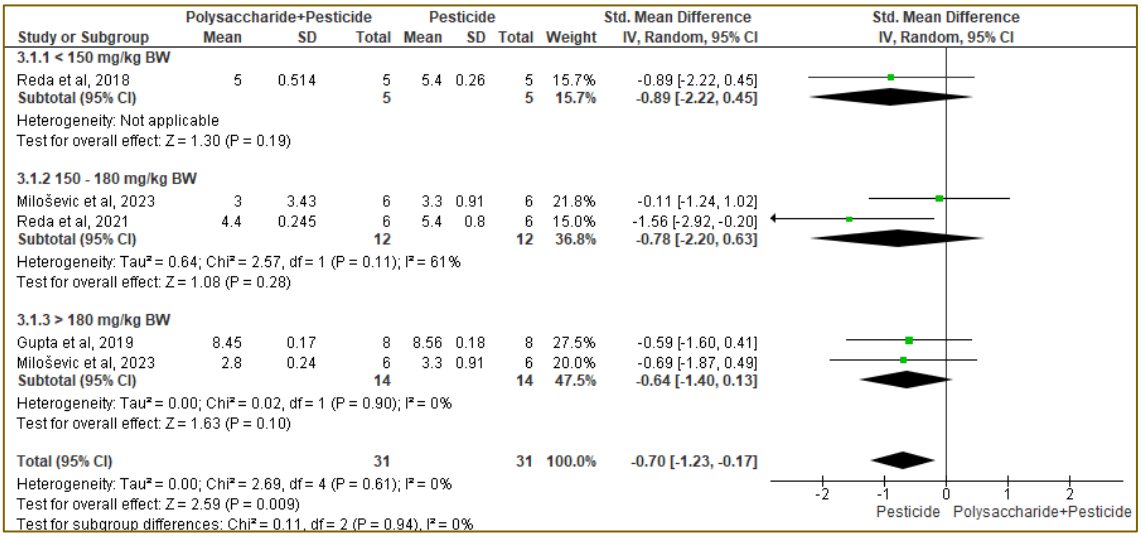

Figure 12. Forest plot of the meta-analysis assessing liver weight in pesticide-exposed animal models, comparing the effects of polysaccharide treatment at different dose ranges: <150 mg/kg BW, 150–180 mg/kg BW, and >180 mg/kg BW, to pesticide-only exposure.

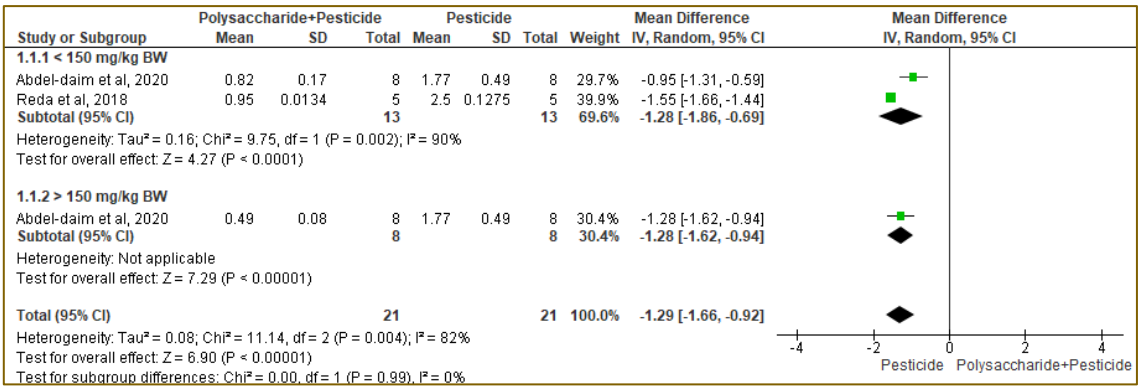

Figure 13. Forest plot of the meta-analysis assessing creatinine levels in pesticide-exposed animal models, comparing the effects of polysaccharide treatment at two dose ranges: <150 mg/kg body BW and >150 mg/kg BW, to pesticide-only exposure.

Urea levels

Two studies evaluated the effect of polysaccharides (fucoidan from *Laminaria japonicum* and pectin) on urea levels in pesticide-exposed animal models, with polysaccharide doses categorized as ≤50 mg/kg BW, 50–100 mg/kg BW, and ≥100 mg/kg BW [17,27]. A significant difference in urea levels was observed only in the ≥100 mg/kg BW dose group (p<0.00001), while no significant differences were found in the ≤50 mg/kg BW (p=0.27) and 50–100 mg/kg BW (p=0.12) groups. The overall effect analysis revealed a statistically significant effect on urea levels (Pooled MD: -18.17; 95%CI: -33.88–[-2.45]; p=0.02). High heterogeneity (I^2=95%; Tau^2=244.30; Chi^2=62.33; p-heterogeneity=0.02) suggests that factors, likely related to varying doses, with substantial true variability in urea levels across studies. Chi^2 value supports significant differences among outcomes. These findings suggest that pesticide exposure increases urea levels, and polysaccharide treatment significantly alleviates this effect in pesticide-exposed animal models (**Figure 14**).

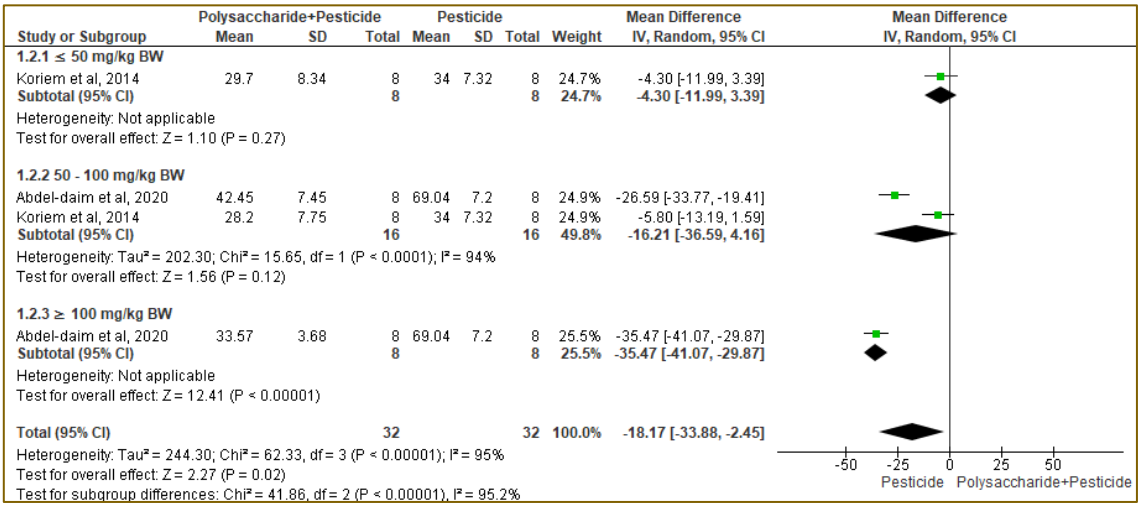

Figure 14. Forest plot of the meta-analysis assessing urea levels in pesticide-exposed animal models, comparing the effects of polysaccharide treatment at different dose ranges: ≤50 mg/kg BW, 50–100 mg/kg BW, and ≥100 mg/kg BW, to pesticide-only exposure.

Kidney weight

Two studies assessed the effect of polysaccharides (pectin and *Nigella sativa* oil) on kidney weight in pesticide-exposed animal models, with doses ranging from <50 mg/kg BW to ≥50 mg/kg BW [27,28]. No significant differences in kidney weight were found across polysaccharide doses (p=0.19 for <50 mg/kg BW; p=0.41 for ≥50 mg/kg BW). The overall effect size revealed a (Pooled MD: -0.30; 95%CI: -2.73–[-2.12]; p=0.81), indicating no statistically significant effect on kidney weight. This suggests that kidney weight was comparable between the groups. High heterogeneity (I^2=85%; Tau²=3.01; Chi²=13.12; p-heterogeneity=0.001) suggests that factors beyond random variation are likely related to differences in study methodologies. The Tau² value indicates moderate to high true variability in kidney weight, while the Chi² value supports the conclusion that significant differences exist among the study outcomes. These findings indicate that polysaccharides preserve kidney weight in animal models (**Figure 15**).

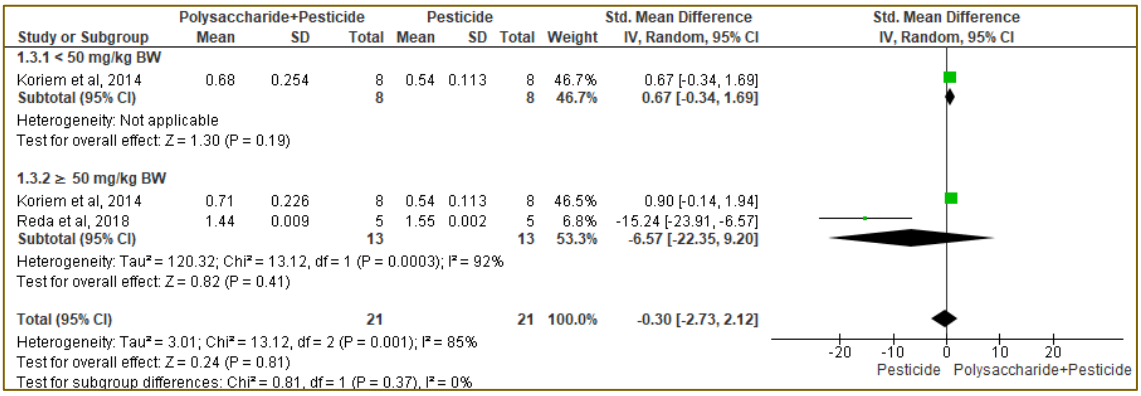

Figure 15. Forest plot of the meta-analysis assessing kidney weight in pesticide-exposed animal models, comparing the effects of polysaccharide treatment at different dose ranges: <50 mg/kg BW and ≥50 mg/kg BW, to pesticide-only exposure.

Effects of polysaccharides on lipid profile in pesticide-exposed animal models

Triglyceride

Three studies evaluated the effects of polysaccharides on triglyceride levels in pesticide-exposed animal models [20,22,28]. Polysaccharide (*Viscum album L.* leaf extract, *Nigella sativa* oil, and okra polysaccharides) doses were categorized as ≤100 mg/kg BW and ≥200 mg/kg BW. A significant reduction in triglyceride levels was observed at a dose of ≤100 mg/kg BW (p<0.00001), whereas no significant effect was noted at a dose of ≥200 mg/kg BW (p=0.43). The

overall effect size revealed a statistically significant impact on triglyceride levels (Pooled MD: -0.32; 95%CI: -0.62–[-0.01]; *p*=0.04), indicating that polysaccharide administration effectively modulates triglyceride levels. However, heterogeneity among studies was extremely high (I^2=98%; Tau^2=0.10; Chi^2=199.22; *p*-heterogeneity<0.00001), suggesting that variability in triglyceride level outcomes was influenced by factors beyond random chance. This substantial heterogeneity likely stems from differences in dosing regimens across the two included studies. The Tau^2 value reflects a low degree of true variability in triglyceride levels, indicating that while heterogeneity exists, the underlying differences are relatively modest. The Chi^2 value further supports the presence of significant variability among study results. These findings underscore the potential of polysaccharides to reduce triglyceride levels, particularly at lower doses (**Figure 16**).

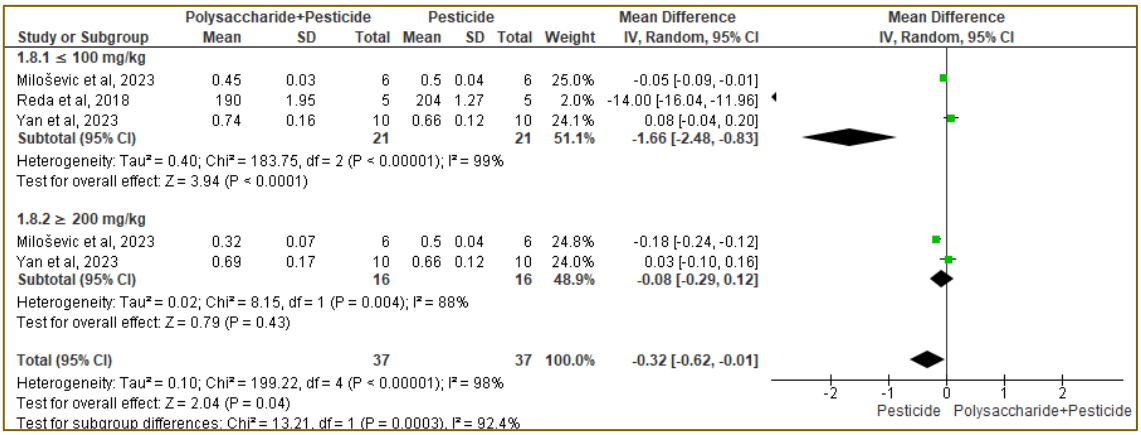

Figure 16. Forest plot of the meta-analysis evaluating triglyceride levels in pesticide-exposed animal models, comparing the effects of polysaccharide doses categorized as ≤100 mg/kg BW and ≥200 mg/kg BW to pesticide-only exposure.

Low-density lipoprotein

Two studies evaluated the effects of polysaccharides (*Nigella sativa* oil 4 mL/kg BW and okra polysaccharides 5 mL/kg BW) on LDL levels in pesticide-exposed animal models [22,28]. The overall effect size revealed no statistically significant effect on LDL levels (Pooled MD: -19.57; 95%CI: -58.03–18.89; *p*=0.32), indicating that polysaccharides do not have a measurable effect on LDL levels. Extreme heterogeneity (I^2=100%; Tau^2=770.07; Chi^2=3719.55; *p*-heterogeneity<0.00001) indicates substantial variability in reported LDL levels, likely due to the limited number of studies included. The high Tau^2 value reflects significant true variability, and the Chi^2 value confirms marked differences among study outcomes (**Figure 17**).

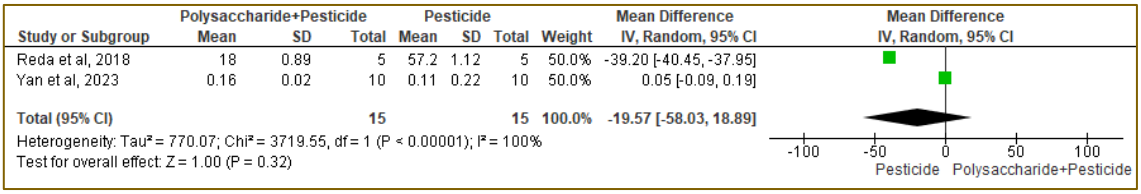

Figure 17. Forest plot of the meta-analysis on low-density lipoprotein (LDL) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

High-density lipoprotein

Two studies evaluated the effects of polysaccharides (*Nigella sativa* oil 4 mL/kg BW and okra polysaccharides 5 mL/kg BW) on HDL levels in pesticide-exposed animal models [22,28]. The overall effect size revealed no statistically significant impact on HDL levels (Pooled MD: -11.44; 95%CI: -32.04–9.17; *p*=0.28), indicating that polysaccharides do not significantly affect HDL levels. The observed high heterogeneity (I^2=100%; Tau^2=220.08; Chi^2=210.35; *p*-heterogeneity<0.00001) suggests that factors beyond random variation influenced the results, with notable variability in HDL level reporting among studies. This heterogeneity is likely due to the limited number of studies (n=2). The Tau^2 value reflects a very high degree of true variability

across studies, while the Chi² value confirms significant differences in study outcomes (**Figure 18**).

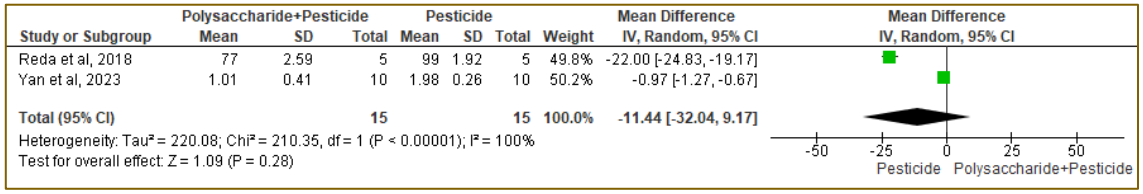

Figure 18. Forest plot of the meta-analysis on high-density lipoprotein (HDL) levels, comparing the effects of polysaccharide treatment to pesticide-only exposure.

Total cholesterol

Three studies evaluated the effects of polysaccharides (*Viscum album L.* leaf extract, *Nigella sativa* oil and okra polysaccharides) on TC levels in pesticide-exposed animal models, with polysaccharide doses categorized as ≤100 mg/kg BW and ≥200 mg/kg BW [20,22,28]. A significant reduction in TC levels was observed with polysaccharide doses ≤100 mg/kg BW (p=0.01), while no significant effect was noted with doses ≥200 mg/kg BW (p=0.31). The overall effect size demonstrated a statistically significant effect on TC levels (Pooled MD: -11.17; 95%CI: -13.79–[-8.56]; p<0.00001). The observed high heterogeneity (I^2=100%; Tau²=8.41; Chi²=1818.40; p-heterogeneity<0.00001) reflects substantial variability in the reporting of TC levels across studies. This variability is likely attributed to the limited number of included studies and differences in the polysaccharide dosage. The Tau² value indicates a pronounced level of true variability, while the Chi² value further substantiates the existence of significant differences among study outcomes (**Figure 19**).

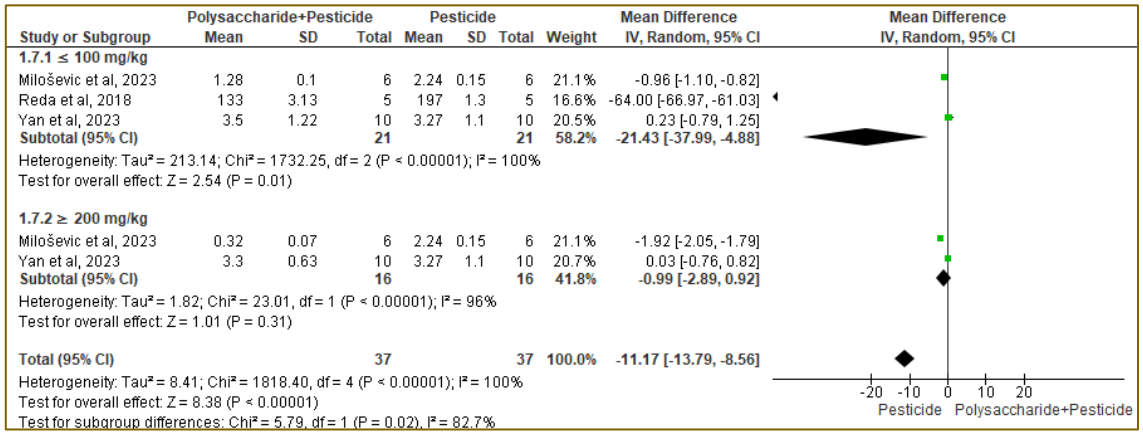

Figure 19. Forest plot of the meta-analysis evaluating total cholesterol (TC) levels in pesticide-exposed animal models, comparing the effects of polysaccharide doses categorized as ≤100 mg/kg BW and ≥200 mg/kg BW to pesticide-only exposure.

Discussion

The present study explored the role of polysaccharides in mitigating toxicity caused by pesticide exposure in animal models. The findings demonstrate that polysaccharides significantly increase antioxidant levels, including CAT (p<0.00001), SOD (p<0.00001), GPx (p<0.00001), and GSH (p<0.00001). Additionally, polysaccharides reduce markers of oxidative stress, such as MDA (p<0.00001) and NO (p<0.0001); as well as kidney injury biomarkers, including serum creatinine (p<0.00001) and urea (p<0.00001). Polysaccharides also improve lipid profiles by reducing TG (p=0.04) and TC (p<0.00001); and liver biomarkers, including AST (p<0.0001), ALT (p<0.005), and ALP (p<0.0001). Additionally, polysaccharides also maintained liver weight (p=0.84) and kidney weight (p=0.37). However, some biomarkers, such as kidney weight, LDL, and HDL, were not significantly affected, probably due to the limited number of studies included in the analysis. There were only two studies that examined the effects of polysaccharides on kidney weight, LDL, and HDL. Overall, the present study highlights the potential role of polysaccharides in mitigating pesticide toxicity.

The significant results observed in some variables of the present meta-analysis could be influenced by several factors, such as the type and dose of polysaccharides used, and the duration of polysaccharide administration. Different polysaccharides may possess distinct biological activities and mechanisms of action. For instance, polysaccharides derived from fungi, such as *Grifola frondosa*, exhibit strong antitumor effects [30], while those derived from plants, such as astragalus polysaccharides, have different immunomodulatory effects [31]. Astragalus polysaccharide has been shown to effectively lower serum levels of AST, ALT, TC, and TG, while also significantly restoring the diversity and community structure of intestinal mucosal bacteria in mice with alcoholic liver disease [31]. In the present study, the polysaccharides used were plant-derived, each with a unique biological mechanism. Therefore, further investigation is needed to optimize the use of polysaccharides for more specific diseases.

The dose of polysaccharide administered can significantly affect the outcomes. Higher doses may result in more pronounced effects but may also increase the risk of side effects or toxicity. In studies involving polysaccharide K (PSK), varying doses were associated with different levels of efficacy in cancer treatment [32]. However, in the present study, no adverse events or side effects were reported. Therefore, it is still unclear whether any doses of polysaccharides contributed to side effects or adverse events. In the present study, almost all ranges of polysaccharide doses resulted in significant effects, except for kidney weight. Further investigation is needed regarding the effects of polysaccharides on kidney function. Additionally, the duration of treatment may also influence the effectiveness of the polysaccharide in eliciting a response. Short-term studies may not fully capture the therapeutic potential or delayed effects that could manifest over a longer period. In several studies on diabetic kidney disease models, longer treatment durations showed more significant improvements in biochemical markers compared to shorter durations [33,34]

The findings of the present study revealed that polysaccharides significantly reduce MDA levels during pesticide exposure. This effect is achieved by increasing antioxidant and reactive sulfur species (RSS) levels in plasma [35]. The mechanism occurs through gut microbiota modulation, which increases RSS species such as *Lachnospiraceae, Ruminococcaceae,* and *Oscillospiraceae*, which produce cysteine persulfide (CysSSH) [35,36]. CysSSH, a persulfide with higher antioxidant capacity than CysSH, GSH, and hydrogen sulfide (H_2S), is induced under oxidative stress, suggesting that polysaccharides improve microbiota resilience to oxidative stress [37,38]. Increased plasma CysSSH levels protect against oxidative stress, reducing MDA levels in polysaccharide-treated rats. The high nucleophilicity of CysSSH and related species allows effective scavenging of oxidants and electrophiles, thus regulating redox signaling [39,40]. These findings are supported by a study involving sodium tetrathionate (Na_2S_4), an RSS compound. In rats with concanavalin-induced hepatitis, Na_2S_4 administration increased plasma RSS levels and reduced MDA levels compared to the control group [35], while the group exposed to pesticides exhibited the highest MDA levels [18,21,24,25]. This suggests that RSS, derived from cystine by gut bacteria, can enter the bloodstream and modulate overall RSS levels in the host.

The increase in CAT and SOD levels, along with the reduction in NO, in rats exposed to both polysaccharides and pesticides, suggests a mechanism by which polysaccharides support REDOX balance through gut modulation [41]. Under normal conditions, free radicals and reactive non-free radicals are maintained at low concentrations through a balance between production and breakdown by antioxidants [42,43]. This equilibrium establishes the reduction-oxidation (REDOX) balance, enabling oxidative signaling while protecting against oxidative damage [42]. Disruption of this balance, leading to excess reactive oxygen species (ROS), can cause irreversible oxidation of lipids, proteins, and DNA [44]. Polysaccharides restore REDOX balance by increasing lactic acid bacteria in the gut, which reduces ROS through antioxidants such as SOD and CAT and produces metabolites such as folate and GSH [42,45]. These metabolites help decrease inflammation by inhibiting pathogen growth and releasing anti-inflammatory substances that reduce pro-inflammatory cytokine secretion from immune cells [43].

Studies have shown that piglets with higher CAT and SOD levels exhibited lower potential of hydrogen (pH) and reduced harmful bacteria, such as *Streptococcus sp*. and *Escherichia-Shigella*, in the colon, alongside decreased levels of pro-inflammatory cytokines, ROS, and NO [46-48]. Lactic acid metabolites contribute to maintaining REDOX balance by reducing NO levels [47]. In normal physiological conditions, baseline NO levels regulate commensal microbe

populations and maintain intestinal epithelial integrity [48-50]. However, elevated NO levels can disrupt gut microbiota diversity and function, promoting the growth of pathobionts [49]. Oxidative changes in the gut environment can reduce immunomodulatory species, such as *Lactobacillus sp*., exacerbating inflammation and contributing to REDOX imbalance [47]. Gut microbiota plays a critical role in maintaining REDOX balance by regulating immune homeostasis and modulating the synthesis of pro-inflammatory and anti-inflammatory cytokines from Th_{17} and T_{reg} cells [42]. *Lactobacillus acidophilus* restores the Th_{17}/T_{reg} balance in colitis and breast tumor models [42,50], while *Clostridia sp*. and *Bacteroides sp*. promote anti-inflammatory responses [51,52]. By balancing Th_{17} and T_{reg} cell activity, these bacteria help prevent excessive ROS production during inflammatory responses, thereby protecting the epithelial layer [53].

Antioxidants in the human body are categorized as non-enzymatic (e.g., glutathione, thioredoxin) and enzymatic [54]. Non-enzymatic antioxidants include glutathione, thioredoxin 1, and thioredoxin 2, with glutathione effectively neutralizing reactive entities such as hydrogen peroxide (H_2O_2), nitrites, nitrates, and benzoates [42]. Enzymatic antioxidants, including CAT, SOD, GPX, and glutathione reductase (GSR), play key roles in oxidative defense. SOD converts superoxide radicals (O_2^-) into H2O2, which catalase further converts into water (H_2O) [55]. GPX reduces H_2O_2 to water and lipid hydroperoxides to stable alcohols, coupled with GSR, which recycles oxidized glutathione [56,57].

The present study found that polysaccharides increased GPx and GSH levels, hypothesized through gut microbiota modulation. Polysaccharides promoted beneficial bacteria (*Enterococcus sp., Bifidobacterium sp., Lactobacillus sp*.) and reduced pathogenic bacteria (*Escherichia coli, Bacteroides sp., Clostridium perfringens*) [58,59]. Additionally, polysaccharides enhanced short-chain fatty acid (SCFA) production, which activates the antioxidant defense system via the Kelch-like ECH-associated protein 1–nuclear factor erythroid 2-related factor 2 (KEAP1-NRF2) pathway [42,60]. NRF2, a key transcription factor, regulates over 200 genes involved in cellular antioxidant defense [61]. SCFAs enhance cell proliferation and oxidative defense by activating free fatty acid receptors (FFARs) and the RAS/RAF/MEK/ERK pathway [42,62,63]. Butyrate, a specific SCFA, activates FFARs, altering the adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratio and activating AMP-activated protein kinase (AMPK), which facilitates the translocation of NRF2 into the nucleus [42,56]. Inhibition of histone deacetylases (HDACs) further enhances NRF2 production, boosting oxidative defense pathways mediated by NRF2 [64]. SCFAs reduce mitochondrial damage from ROS, boost antioxidants such as GPx and GSH, and protect the mitochondrial respiratory chain. Thus, SCFAs play a crucial role in defending cells against oxidative stress [60].

Elevations in liver function markers indicate that pesticides induce hepatotoxicity, oxidative stress, and inflammation in the control group [65]. Polysaccharide administration, due to its antioxidant and anti-inflammatory properties, offers significant protection against liver damage caused by pesticides [66]. This supplementation reduces oxidative stress, alleviates inflammation, and promotes repair of liver tissue [66,67]. Pesticides generate excessive free radicals, leading to oxidative stress, liver cell damage, inflammation, and liver swelling, ultimately increasing liver weight [68,69]. Polysaccharides, by mitigating oxidative stress and inflammation, may protect against pesticide-induced increases in liver weight [68].

Polysaccharide administration reduces ROS and oxidative stress in kidney cells, enhancing glomerular filtration rate and lowering creatinine levels [70]. Additionally, polysaccharides regulate inflammation and apoptosis pathways in the kidney [71]. By reducing inflammation and preventing kidney cell death, polysaccharides contribute to improved kidney function and lower creatinine levels [70]. Increased serum urea levels indicate kidney damage, with the pesticide group exhibiting greater susceptibility to renal damage than the polysaccharide group, suggesting that polysaccharides offer protective effects against pesticide-induced kidney injury [72].

Polysaccharides, as antioxidants, mitigate inflammation induced by increased oxidative stress, thereby protecting kidney cells and enhancing glomerular filtration rate, which reduces serum urea levels [70,73,74]. Polysaccharides also decrease proteinuria, an important indicator of kidney health, further contributing to lowered serum urea levels [72,74,75]. Kidney inflammation can lead to fibrosis and increased kidney weight due to fibrotic tissue accumulation

[67]. Polysaccharides reduce extracellular matrix production, a key factor in renal fibrosis, and inhibit the TGF-β/Smad pathway, which plays a crucial role in glomerular fibrosis [72,76]. This reduction helps protect glomerular filtration function and reduces kidney weight [77].

Although the present meta-analysis found the LDL reduction to be non-significant due to the limited number of included studies, the reduction remains greater in the intervention group. Therefore, this result still aligns with the effect of polysaccharides in improving lipid profile control by reducing TG, LDL, and TC levels [78]. Elevated TG levels contribute to increased fat accumulation, exacerbating inflammation and increasing the risk of various diseases [78]. Elevated LDL levels promote "bad" cholesterol accumulation, triggering chronic inflammation, while excessive TC can cause tissue damage and inflammation, adversely affecting organs such as the kidneys, liver, and heart [19,28]. Polysaccharides reduce cholesterol absorption by increasing bile acid excretion, leading to lower blood cholesterol levels [79,80]. Additionally, polysaccharides possess anti-inflammatory properties that enhance lipid metabolism and prevent dyslipidemia, characterized by an imbalance in blood lipid levels [81].

Under normal conditions, HDL levels are typically higher or increased compared to other components of the lipid profile, and a decrease in HDL is often associated with higher levels of inflammation [82]. However, the present meta-analysis showed a non-significant decrease in HDL levels in the polysaccharide intervention group. These findings suggest that polysaccharides may contribute to slightly lower HDL levels under certain conditions, but the decrease is not significant, and the potential negative effects are minimal and comparable to normal conditions [83]. Nevertheless, this conclusion cannot be definitively confirmed due to the limited number of studies included in the meta-analysis.

Another possible reason for the decrease in HDL levels is its role as an adaptive response to counteract pesticide-induced damage [84]. HDL facilitates the transport of cholesterol from tissues to the liver for excretion, thereby reducing cholesterol accumulation [84]. Certain pesticides can alter lipid metabolism and potentially increase HDL synthesis. Conventional farmers who use pesticides have been shown to exhibit higher HDL levels compared to organic farmers [85]. Additionally, exposure to organophosphate pesticides has also been associated with increased HDL levels [86]. Therefore, the lack of an increase in HDL levels in the polysaccharide group may suggest that lipid metabolism and cholesterol accumulation are already within normal limits.

The findings in the present study suggest that polysaccharide interventions may be a potentially good alternative for reducing organ damage due to pesticide exposure. With its effect on reducing inflammation, marked by a decrease in MDA and NO levels accompanied by an increase in antioxidant components (CAT, SOD, GPx, and GSH), polysaccharides support the prevention of organ damage related to inflammation [42]. Administration of polysaccharides also supports improved kidney and liver function. In terms of improving kidney function, polysaccharides can increase glomerular filtration rate, reduce serum creatinine levels, and reduce urea levels, which shows a protective effect against kidney injury due to toxicity [70,72]. This effect is supported by its ability to reduce inflammation and prevent renal fibrosis by inhibiting the transforming growth factor-β/Smad (TGF-β/Smad) pathway [72,76]. The effect of improving liver function is characterized by polysaccharides that show the ability to reduce levels of liver damage biomarkers, such as ALT, AST, and ALP, while reducing inflammation and repairing damaged liver tissue [87]. Polysaccharides also protect the liver from hepatotoxicity by reducing oxidative stress and preventing liver enlargement caused by inflammation [88].

Modulation of the gut microbiota by polysaccharides contributes to the reduction of systemic oxidative stress and inflammation, further providing a balancing effect on overall health [89]. Polysaccharides, through impacts on both gut microbiome and systemic inflammation, exhibit promising potential as adjunctive therapies. The ability to protect liver and kidney functions makes polysaccharides particularly valuable for individuals at high risk, such as farmers and families regularly exposed to pesticides. These individuals often suffer from chronic oxidative stress and organ dysfunction due to prolonged pesticide exposure. Therefore, polysaccharides could serve as a safe and effective therapeutic option, providing a non-toxic alternative to support liver and kidney health, prevent further damage, and manage existing conditions associated with

pesticide exposure. However, this potential therapeutic role warrants further investigation to fully establish the clinical efficacy and applicability in such vulnerable populations.

The present systematic review and meta-analysis have several limitations. First, the types of pesticides and their corresponding doses vary, making it difficult to identify specific pesticides that may lead to dysbiosis. Second, the meta-analysis results exhibit high heterogeneity, which may be attributed to differences in population size, intervention duration, and dosage. Third, sensitivity analysis could not be conducted due to the insufficient number of studies available. Future research should aim to conduct systematic reviews and meta-analyses focusing on specific types of polysaccharides or organophosphates, as this would provide a clearer understanding of the effects of these substances and offer more precise insights. Additionally, further studies should prioritize high-quality randomized controlled trials with larger sample sizes to strengthen the robustness of the findings.

Conclusion

Polysaccharides demonstrate significant potential in improving antioxidants measured by catalase, superoxide dismutase, glutathione peroxidase, and glutathione, reducing oxidative stress measured by malondialdehyde and nitric oxide, repairing biomarkers of organ damage, liver, and lipid profiles measured by serum creatinine, urea, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, triglycerides and total cholesterol, and maintaining liver and kidney weights in pesticide-exposed animal models. Polysaccharides show potential as adjunctive therapies by modulating the gut microbiome and systemic inflammation, particularly for individuals at high risk, such as farmers and their families exposed to pesticides. However, future human studies are necessary to further assess the efficacy and safety of polysaccharides in individuals at high risk due to pesticide exposure.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools and methodologies in the following capacities of which AI-based language models ChatGPT was employed in the language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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