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Review Article

The Imapact of Paracetamol on the Excretory System: A Review of Toxicity and Protective Strategies

Punam Bante [1], Shikha Sethiya [2], Mangala Thakare [3], Varsha Dhurvey [4*]

[1]Department of Zoology, RTM Nagpur University, Nagpur, Maharashtra, India
[2]Department of Zoology, RTM Nagpur University, Nagpur, Maharashtra, India
[3]Department of Zoology, RTM Nagpur University, Nagpur, Maharashtra, India
[4]Department of Zoology, RTM Nagpur University, Nagpur, Maharashtra, India

**Corresponding Author:* ✉

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Abstract— Paracetamol, a painkiller and antipyretic, works well for pain and fever. But its availability and perceived safety puts us at risk of accidental overdose which can cause liver damage, kidney failure, and other side effects. Paracetamol works by inhibiting COX-2 enzymes, reducing prostaglandin production, and targeting the hypothalamus to relieve pain, inflammation, and fever. But overdose can cause severe kidney damage and impairment leading to acute and chronic renal dysfunction. Studies have shown that paracetamol administration can cause nephrotoxicity characterized by histopathological changes, oxidative damage, and apoptosis. Long term and repeated intake can cause kidney dysfunction, damage, and ultrastructure defects. Fortunately, several compounds have been found to counteract paracetamol's toxic effects including *Nigella sativa*, nitric oxide, alpha- lipoic acid, quercetin, curcumin, and antioxidants. These substances have been shown to reduce oxidative stress, inflammation, and kidney damage caused by paracetamol overdose. In summary, while paracetamol is widely used as an effective painkiller, its potential for overdose and toxicity requires cautious use and awareness of the risks. The identification of compounds that can counteract paracetamol's toxic effects is a promising avenue to reduce paracetamol-induced kidney damage and safe treatment.

Keywords— Paracetamol, Histological alteration, Biochemical analysis, Oxidative stress enzymes, Urine and plasma analysis, Mitigating agent.

1. Introduction

Paracetamol is also known as 4-Aminophenol, N-Acyl-aminophenol, 4- Hydroxyacetanilide, and Tylenol (brand name). Paracetamol (acetaminophen) has been around for over 100 years. First synthesized in 1877 it wasn't until the 1960s that it became an over-the-counter medication it is an antipyretic and analgesic for headaches, fever, and minor ailments. It is used in cold and flu treatments and can be combined with opioids for severe pain management like post-surgical pain. Overdose can cause serious side effects like liver damage, skin rashes, and pancreatic inflammation [1, 2]. Paracetamol is an over-the-counter medication for fever and pain relief available in many forms [3, 4].

Paracetamol overdose is one of the top causes of acute liver failure and also can cause renal failure (damage to the kidneys) in humans [5]. Paracetamol inhibits the enzyme that is responsible for the synthesis of prostaglandins, which induce dilation of the blood vessels and pain. By inhibiting the production of prostaglandins, paracetamol eases pains such as headaches, migraine, muscle pain, toothache, and cramps during menstruation. It also lowers fever due to bacterial or viral infections. With few side effects, paracetamol is safe for the majority of people, including children and the elderly, making it a general and dependable pain reliever [6].

Overdose of paracetamol is a prevalent hazard because it is so widely available and perceived to be safe. With almost 60 million Americans consuming it each week, the risk comes from its commonality. Paracetamol frequently appears in combination drugs along with other drugs, e.g., diphenhydramine and opioids, whose presence is not known to the user. Such veiled inclusion in combined drugs raises the threat of unintentional overdose [7]. Paracetamol adult dose is 1000mg every 4 hours, to a maximum daily dose of 4g, but for children, it depends on age [8]. More than 4g daily raises the risk of toxicity, and overdoses over 10g increase major risk [9].

1.1 Chemical structure

Paracetamol's molecular structure, such as its acetamido and phenolic hydroxyl groups, is central to its chemical and

biological activities. Intermediate activating properties of the acetamido group are due to competing resonance with lone pair delocalization, whereas the phenolic hydroxyl group modifies conjugation and metabolism. Such a complex interplay controls paracetamol's electronic properties, chemical reactivity, metabolic routes, and pharmacological profile [10].

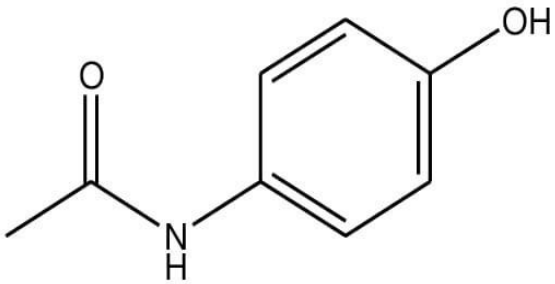

Figure 1. Chemical Structure of Paracetamol [75]

2. Methodology

2.1 Literature survey strategy

A thorough review of the literature was carried out, including experimental and non-experimental studies. Using leading internet databases such as Google Scholar, Science Direct, WHO, PubMed, Research Gate, and peer-reviewed review articles from 2000 to 2024 were identified and compared. The combined evidence from the studies clearly points to the fact that paracetamol is a significant health risk to human beings. The results of this review bring out the far-reaching implications of paracetamol consumption, underlining its harmful effect on human health as well as the imperative of vigilance, more research, and informed choice.

2.2 Data extraction

The studies that appeared in the search engines were the first to be scanned. Relevant studies were imported into Microsoft Excel and totaled according to their abstract, purpose, and conclusions.

3. Results and Discussion

3.1 Mode of Action-

Paracetamol mechanism, though not fully understood, likely involves inhibiting cyclooxygenase-2 (COX-2), similar to traditional Non-steroidal Anti-inflammatory Drugs (NSAIDs). NSAIDs block COX enzymes, preventing arachidonic acid conversion to prostaglandin G2 (PGG2), and subsequently to PGH2. PGH2 is then converted to various prostaglandins by local tissues. Paracetamol's COX-2 inhibition may selectively target this pathway, reducing pain and inflammation [11]. It primarily inhibits brain cyclooxygenase and potentially blocks central nervous system prostaglandin production. This relieves pain and fever. Additionally, paracetamol directly targets the hypothalamus, reducing body temperature [12]. Research suggests it acts on both the peripheral and central nervous systems. It may involve inhibiting pain signaling pathways in the brain and spinal cord, as well as blocking pain production at injury sites [13].

3.2 Effects of Paracetamol on Kidney

The kidneys play a crucial role in maintaining the body's fluid, electrolyte, acid- base, and waste balance, but excessive strain from drug overdoses can impair their function, leading to complications [14]. Adhering to recommended dosages is crucial, as overdosing can cause kidney damage in animal models [15]. Paracetamol induced liver and kidney damage is primarily caused by oxidative stress and free radical production triggered by drug toxicity [16]. At therapeutic doses, paracetamol undergoes liver metabolism and is excreted by the kidneys [17]. Paracetamol, however, is known to cause both acute and chronic kidney injury, where large doses induce necrosis and damage to the proximal tubule, while long-term exposure results in persistent renal impairment [18]. Additionally, NSAIDs can impact renal function, particularly in individuals with pre- existing risk factors, by reducing prostaglandin production and affecting blood flow and function [19].

Animal studies suggest that excessive metabolism of paracetamol by cytochrome P-450 enzymes causes renal tubule damage in conjunction with reduced glutathione levels [20]. A number of studies have shown that administration of high paracetamol doses causes renal damage in mice. This is an indication that the risk of renal toxicity as a consequence of paracetamol overdose is a reality [21]. Paracetamol poisoning may cause serious kidney injuries, including acute tubular necrosis and acute renal failure [22]. Paracetamol poisoning results in liver and kidney injury of the type referred to as hepato- nephrotoxicity in both humans and animals [23, 24].

3.3 Effects of Paracetamol on Bladder

The bladder holds urine that the kidneys secrete and empties from the body via the urethra, a vital part of the urinary system. Bladder cancer is ranked 4th in men and 10th in women among the leading cancers [25]. It has been established that analgesic consumption has different implications for the risk of kidney and bladder cancer. The use of paracetamol or aspirin has been shown to cause the hazard of kidney failure to rise by 2.5 times [26]. COX-2 inhibition by paracetamol could selectively inhibit this pathway and decrease pain and inflammation [11]. Paracetamol weakly inhibits both COX-1and COX-2 enzymes, but its efficacy in reducing PG production is more significant under some circumstances. In particular, paracetamol is better at inhibiting PG synthesis when arachidonic acid levels are low, and in intact cells compared to disrupted cell systems. Paracetamol inhibition of PG synthesis is also more significant in COX-2 dependent pathways, which are responsible for pain and inflammation. In total, the precise mechanism by which paracetamol affects COX enzymes is unknown but is thought to contribute to its anti-inflammatory and analgesic effects [27].

The COX-2 enzyme is excessively active in the majority of bladder tumors, which stimulates tumor growth. It inhibits apoptosis, induces angiogenesis, and interferes with the TP53 tumor suppressor gene, causing cell division without regulation. This enzyme is involved in bladder cancer development and progression and is thus an ideal target for prevention and cancer treatment [28]. COX-2 has been

associated with aggressive bladder cancer, indicating advanced tumor stages and abnormal cell proliferation [29].

Bladder cancer and paracetamol research has produced conflicting results. Some studies suggest heavy paracetamol use may raise the risk of bladder cancer, but most studies found no significant link. Conversely, NSAIDs, except pyrazolone derivatives, reduce the risk of bladder cancer, whereas paracetamol can raise it [30]. Excessive use of paracetamol has been weakly linked to an enhanced risk of renal cancer [31]. Conversely, paracetamol has also been discovered to have anticancer actions apart from analgesia and potentially benefits the therapy of non-muscle invasive bladder cancer [32]. Regular analgesic consumption has also been linked with reduced risk for bladder cancer and is thought to have a preventive effect against bladder cancer. The regular intake of non-aspirin NSAIDs has been associated with decreased bladder cancer risk, and the protective effect was independent of genetic susceptibility [33].

3.4 Histology

Paracetamol administration in rats caused significant biochemical and histological changes, including increased serum urea and creatinine levels, degeneration of the tubular system, and dilation of tubules filled with hyaline casts, indicating nephrotoxicity associated with oxidative damage and apoptosis [34]. Study shows infiltration, congestion glomerulus, and tubular damage in the kidney. The histopathological changes in the liver, as well as the kidney tissue, reveal details about the potential hazards associated with increasing liver, renal, and neurological damage caused by long-term, repetitive paracetamol intake [35]. Long-term paracetamol treatment resulted in histopathological injury to the kidney and spleen of the adult albino mouse, with enhanced interstitial space, damaged epithelial cells, tubular structure degeneration, and increased serum creatinine and blood urea content, reflecting kidney impairment and paracetamol over consumption toxicity [36]. Paracetamol treatment during pregnancy has toxic implications on maternal and fetal tissues, involving renal damage, ultrastructure alterations, and necrosis. Histopathological studies proved renal injury in treated mother rats and more pronounced injury in gestation-extended rats. Such results reiterate that extra vigilance should be exercised while prescribing paracetamol to pregnant women [37, 38].

3.5 Biochemical Analysis

Paracetamol has been established to induce severe damage to different organs and tissues. Research has established that paracetamol augments oxidative stress and reduces antioxidant defenses, causing tissue injury. In particular, paracetamol has been proven to augment thiobarbituric acid-reactive substances, bilirubin, urea, and creatinine, but reduce superoxide dismutase, glutathione peroxidase, glutathione S-transferase, and catalase levels. Also, paracetamol has been shown to induce renal impairment, as indicated by elevated serum urea, uric acid, creatinine, and lipid peroxide levels [39, 40]. Elevated serum creatinine and blood urea levels, and reduced packed cell volume, haemoglobin, and red blood cell counts have also been reported in other studies [36, 41]. Effect of paracetamol on rat liver and kidney function following chronic alcohol use, and discovered that paracetamol overdose led to the production of increased bilirubin and urea and reduced albumin levels, signifying liver and kidney injury, whereas haematological tests were unaffected [42]. The research established that paracetamol greatly elevated creatinine and blood urea nitrogen levels, signifying serious kidney injury [43].

3.6 Oxidative Stress Enzymes

Paracetamol induced nephrotoxicity by causing renal injury, elevating blood urea nitrogen, creatinine, and malondialdehyde levels. Taxifolin, on the other hand, had antioxidant activity, enhancing glutathione peroxidase, glutathione reductase, and glutathione levels [44]. Paracetamol overdose has been found to temporarily increase certain urine enzymes, including glutathione transferase-alpha (alpha-GST), glutathione transferase-pi (pi-GST), N-acetyl beta-D-glucosaminidase (NAG), N-acetyl beta-D-glucosaminidase iso-enzyme (NAG-B), beta-galactosidase (β-GAL), beta-glucuronidase (β-Gr) and others, after toxic paracetamol doses, but no acute kidney failure occurred [45]. Quercetin and curcumin protected against paracetamol-induced oxidative injury in rats, improving antioxidant enzymes and liver/kidney functions. Curcumin showed more pronounced effects than quercetin [39].

3.7 Urine and Plasma Analysis

Five studies developed and validated analytical methods for quantifying paracetamol in biological samples. Jensen *et al.* (2004) [46] used liquid chromatography to analyze human urine, while Hewavitharana *et al.* (2008) [47] employed HPLC- MS/MS to measure paracetamol metabolites in mouse urine and biological fluids. Soysa and Kolambage (2010) [48] developed a rapid HPLC/UV method for simultaneous urine, plasma and serum analysis. Adriana *et al.* (2017) [49] investigated an HPLC-PDA method for measuring paracetamol levels in arthritic rat plasma. Marie *et al.* (2019) [50] developed a CE-MS method to quantify acetaminophen and its primary metabolites in urine, revealing changes in metabolism post-liver surgery. All methods demonstrated high accuracy and sensitivity.

Urinary biomarkers kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin demonstrate high accuracy in diagnosing acute kidney injury, achieving 90% accuracy and perfect precision, making them a reliable diagnostic tool [51]. Paracetamol overdose affects electrolyte levels in blood and urine, causing a decrease in potassium levels with increasing paracetamol concentrations [52]. Urine and blood samples from patients who overdosed on paracetamol found temporary increases in certain urine enzymes, but no acute kidney failure [45].

3.8 Case Study

Studies have investigated the effects of paracetamol overdose on kidney function and serum electrolytes in patients. Patients with kidney failure were more likely to have taken aspirin and paracetamol than healthy controls, with 25% of patients taking paracetamol and 37%taking aspirin [26]. A study of 8 patients

who took a large dose of paracetamol found temporary increases in certain urine enzymes, but no acute kidney failure [45]. Among 31,654 incident renal replacement therapy patients in Australia, 10.2% had analgesic nephropathy [53]. A case study of a 39-year-old man disclosed that overdose of paracetamol caused severe kidney injuries [54]. A 22-year-old patient, after an overdose of paracetamol, presented with acute renal impairment [55]. In research on patients admitted to the Poison Control Centre, acute paracetamol overdose did not show any significant effect on kidney function or serum electrolytes [56]. Examined 20 cases of acute kidney injury caused by paracetamol overdose, including three children and adolescents who were treated with N-acetyl cysteine. Even after treatment, the patients developed symptoms such as abdominal pain, vomiting, and backache, which underscores the need for effective and timely paracetamol overdose treatment [57]. Short- term use of paracetamol (7-30 days) was found to cause a rise in kidney disease risk in the case study [58].

3.9 Transplant and Replacement Therapy

For instance, most patients suffering from analgesic nephropathy, including those afflicted by paracetamol-induced hepatotoxicity, might need renal replacement therapy or liver transplants to treat their condition [53]. Liver transplant has been noted to enhance survival in patients with significant acute liver and kidney injury secondary to paracetamol poisoning, with significantly lower mortality of 20% in the patients who underwent liver transplant compared to 58% in the patients who did not [59]. Also, patients who underwent liver transplantation had improved outcomes, as one study reported excluding 54 patients who underwent liver transplantation from the mortality rate analysis [60]. 74 patients with paracetamol-induced liver damage, including 7 with no liver or kidney damage, 42 with spontaneous recovery, 16 who were fatal, and 9 who underwent a liver transplant [61].

3.10 Mitigating Factor

Histological examination of the kidneys revealed severe damage in the paracetamol group, whereas the Taxifolin group showed only mild changes, demonstrating its renoprotective benefits [44]. Combination therapy with rosuvastatin and paracetamol was found to increase liver damage and kidney histopathologic alterations, despite unchanged serum liver functions, and also significantly elevated inducible nitric oxide synthase activity in both liver and kidney tissues [62]. Betanin supplementation significantly reversed biochemical and histochemical alterations caused by paracetamol and diclofenac, including oxidative stress, brain DNA damage, and altered brain histopathology [63]. *Ulva fasciata*'s ethanolic extract and chloroform fraction restored kidney architecture, as confirmed by histology, and normalized biochemical markers, including creatinine, urea, bilirubin and liver enzymes, in rats with paracetamol-induced nephrotoxicity and hepatotoxicity [64]. Biochemical results from two studies showed protective effects against acetaminophen-induced toxicity, where pretreatment with aminoguanidine, gadolinium chloride, or oleanolic acid, and daily administration of alpha-lipoic acid (25mg/kg or 100mg/kg) reduced biochemical markers of toxicity, including liver enzymes alanine transaminase and aspartate transaminase and bilirubin levels, as well as kidney function tests (creatinine, urea) [65, 66].

Nigella sativa extract reduced biochemical markers of kidney damage, including creatinine and serum urea levels, in paracetamol-treated rats, indicating a protective effect against nephrotoxicity [17]. Chrysin protected kidney function by lowering serum renal toxicity markers and enhancing antioxidant enzyme activities, thereby exhibiting protective effects towards paracetamol-induced kidney toxicity in rats [67]. Amlodipine on paracetamol-induced acute kidney toxicity in rats and concluded that paracetamol had damaged kidney function, and raised levels of creatinine and blood urea level, whereas amlodipine protected the kidneys and restored these levels by decreasing oxidative stress and enhancing antioxidant activity [43]. Scientists explored the effect of vitamin C on paracetamol-induced kidney and liver injury in rats and found that vitamin C pre- treatment or co-treatment efficaciously counteracted paracetamol toxicity, as indicated by noteworthy weight gain among treated rats [68]. Antioxidant mechanisms of *Amblygonocarpus androgenesis Stem Bark* Extract (AEAASB) in preventing paracetamol-induced renal and hepatic failure in rats. The findings revealed that AEAASB treatment lowered toxic chemicals, and oxidative stress indicators, and raised antioxidant defence, thus efficiently inhibiting paracetamol-induced tissue injury in both the liver and kidney, supporting its potential protection against hepatic nephrotoxicity [69].

Magnesium hydride against paracetamol-induced acute kidney injury in mice. The outcomes indicated that magnesium hydride guarded against paracetamol-acute kidney injury by enhancing renal function, attenuating oxidative stress, suppressing inflammation, inhibiting apoptosis, and blocking the TXNIP/NLRP3/NF-KB signalling pathway, indicating its therapeutic potential in preventing paracetamol-induced kidney injury [70]. Losartan markedly reverted oxidative and inflammatory harm, alleviated histopathological alterations in liver and kidney tissue, and showed protective effects against acetaminophen toxicity, as evidenced by its potential therapeutic importance in guarding against acetaminophen-induced liver damage [71]. Amlodipine therapy effectively safeguarded the kidneys through the attenuation of oxidative stress and enhancement of antioxidant activity, hence enhancing kidney function. These results indicate that amlodipine could be an effective therapeutic agent in the prevention of renal injury brought on by paracetamol [43]. Treatment with 4-Methylpyrazole efficiently decreased toxic metabolites of paracetamol, blocked the depletion of antioxidants, and shielded against renal injury, emphasizing the therapeutic advantages of 4MP in the prevention of paracetamol-induced nephrotoxicity [72]. Arjunolic acid prevents paracetamol-induced kidney damage by inhibiting excessive production of nitric oxide, maintaining levels of antioxidants, and inhibiting tumor necrosis factor-alpha production, which prevents renal tissue damage due to acute paracetamol toxic [73]. *Zingiber*

zerumbet extract prevents paracetamol-induced oxidative stress and nephrotoxicity in rats. The extract notably inhibited renal cellular damage, thereby preventing the damaging effects of paracetamol on the kidney [74]

Table 1. Effect of paracetamol and their mitigating factors

Doses and Duration	Parameters	Interference	Reference
Rat (50mg/kg, oral), GdCl3 (10mg/kg, intramuscular), or oleanolic acid (25mg/kg)	Biochemical and histopathological	Gadolinium chloride, aminoguanidine, and oleanolic acid protected rats from acetaminophen-induced liver and kidney damage.	Abdel *et al*., 2007
Rat, Alpha-lipoic acid (25mg/kg) Paracetamol (750mg/kg), 2.4 pmol, 1.2 pmol, and 1.2 pmol,	Biochemical and histopathological	Alpha-lipoic acid (100mg/kg) pre-treatment mitigated acetaminophen (2.5g/kg)- induced hepatotoxicity and nephrotoxicity in rats.	Abdel *et al.,* 2008
Rats	Histological analysis	Quercetin and curcumin were found to have protective effects on liver histology and liver and kidney functions.	Yousef *et al.,* 2010
Rats, 400 mg/kg *Zingiber zerumbet* extract, 750 mg/kg Paracetamol	Histological analysis	*Zingiber zerumbet* extract 400 mg/kg dose with paracetamol found to be more productive than 200 mg/kg low dose.	Abdul *et al*., 2012
Rats, *Nigella sativa* (250, 500, 1000 mg/kg)	Histopathology	Paracetamol increased serum urea and creatinine levels and *Nigella sativa* reduced these levels.	Canayakin *et al.,* 2016
Rats, 3 group N=6, 1000 mg/kg	Histology, antioxidants and enzymes	Severe damage in PARG and mild changes in TXFG, demonstrating Taxifolin's Renoprotective benefits.	Topal *et al*., 2016
Rats, 25 or 50 mg/kg/day single oral dose ofParacetamol 6 days	Apoptosis and autophagy marker, antioxidant enzymes	CR protects the kidney by lowering serum renal and boosting antioxidant enzyme activity.	Kandemir *et al.,*2017
24 male albino rats (180–190 g)	Hormonal and histological analysis	Nubiq exhibited greater efficacy in lowering inflammation and oxidative stress.	Fadda *et al.,* 2019
40 Rats, Paracetamol 400mg/kg/day 28 days	Histopathology, hormonal analysisand antioxidant enzymes	Paracetamol and diclofenac treatments caused significant harm, decreasing hormone levels and increasing oxidative stress, DNA damage, and altering brain structure.	Motawi *et al.,* 2019
Mice, 300 - 600 mg/kg (2,6,or 24 hours)	Mice metabolites	Prevent antioxidant depletion & protect against kidney damage	Akakpo *et al.,* 2020
40 Rats, 500 mg/kg Vitamin C, and 500 mg/kg Paracetamol	Weight response and antioxidant enzymes	Paracetamol caused weight loss, and liver/ kidney damage in rats; Vitamin C pre-treatment/co-treatment reversed effects, showcasing protective antioxidant properties.	Abdalally *et al.,* 2021
30 Rats, Amlodipine (10mg/kg), Paracetamol (2g/kg)	Antioxidant enzymes and hormonal analysis	Amlodipine protects kidneys from paracetamol-induced damage by effectively reducing oxidative stress and boosting antioxidant activity, preventing renal toxicity.	Karatas *et al.,* 2022
Silymarin (100mg/kg) *Solanum anomalum* extract (452/678mg/kg) for 8 days.	Histopathology	Mitigating effect of *Solanum anomalum* fruit extract on kidney damage brought on by paracetamol.	Offor *et al.,* 2022
Rats, Paracetamol (1000 mg/kg) and other drugs (125, 250, and 500 mg/kg) 8 days	Histochemical	AEAASB effectively prevented paracetamol-induced tissue membrane cellular damage in both the liver and kidney.	Baponwa *et al.,* 2022
Rats were divided into 5 groups, Paracetamol (600 mg/kg)	Histological analysis	*Ulva fasciata*'s ethanolic extract and chloroform fraction: normalized kidney and liver markers, replenished glutathione (GSH), restored kidney architecture.	Sohai *et al.,* 2022
24 Mice (Paracetamol 500 mg/kg,i.p.) 3 days	Histological analysis and apoptosis	Improving renal function, reducing oxidative stress, inhibiting inflammation, suppressing apoptosis and inhibiting the TXNIP/NLRP3/NF-KB signaling pathway.	Si *et al.,* 2024
Mice, 500 mg/ kg Paracetamol	Histopathology	Changes in liver and kidney tissues, demonstrating its protective effects against paracetamol-induced toxicity.	Sahin *et al.,* 2024

4. Conclusion and Future Scope

This research brings into perspective the impact of paracetamol on human health, specifically on kidney and liver tissues. Vascular congestion, glomerular haemorrhage, and kidney damage were determined by histopathological examination, and creatinine and serum urea levels were significantly elevated by paracetamol, signifying renal damage. The long-term consumption of paracetamol caused liver, renal and neurological injury, hormonal imbalance, oxidative stress, DNA damage, and brain structural change. These results point out the hazards of long-term consumption of paracetamol toxic to human health. *Nigella sativa*, nitric oxide, alpha-lipoic acid, quercetin and curcumin, *Zingiber zerumbet* Smith ethyl acetate, chrysin, nano ubiquinone, allicin, ascorbic acid, betanin, 4-methylpyrazole, *Ulva fasciata*, green alga and magnesium hydride supplementation prevented these harmful effects of paracetamol. The results of these studies advance our knowledge of the possible negative health effects associated with prolonged paracetamol use as well as the potential advantages of nutritional treatments in reducing or eliminating these effects, which in turn helps to guide therapeutic and public health initiatives.

Data Availability
The data supporting the study's findings are readily available on Google Scholar and PubMed. The associated author can additionally provide the data set created during this time upon reasonable request.

Conflict of Interest
The authors declare no conflicts of interest in the preparation of this manuscript.

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Authors' Contributions
Punam Bante researched literature, conceived the study and analyzed the data. Shikha Sethiya and Mangala Thakare made a substantial contribution to the concept and visualization of this review article. Varsha Dhurvey offered validation and supervision. All authors offered insightful criticism and contributed to the development of the final manuscript and have read and approved the manuscript's published version.

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AUTHORS PROFILE

Punam Bante completed her B.Sc. degree from Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, in 2023 and she is currently pursuing her M.Sc. in Zoology from the Post Graduate Teaching Department of Zoology, an autonomous department at Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur. She is currently working on her minor project at RTM Nagpur University, Nagpur.

Shikha Sethiya earned her B.Sc. and M.Sc. degree in Zoology from Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, in 2019 and 2021, respectively. As a research scholar, she is presently working on her PhD at RTM Nagpur University's Department of Zoology. "The effects of butylated hydroxyanisole on male reproductive organs" is one research topic of focus.

Mangala Thakare earned her M.Sc. in Zoology from Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, in 2008 and later obtained her PhD in Zoology from the same institution in 2017.She has been serving as an Assistant Professor in the Department of Zoology since 2012, with 12 years of teaching experience.Having published nine research papers in reputable national and international publications, she has an exceptional research record and has been a life member of the Indian Science Congress (ISC) since 2023.Her primary research interests include fluoride toxicity, reproductive biology, and toxicology.

Varsha Dhurvey has finished her M.Sc. and Ph.D. from RTM Nagpur University, Nagpur, in 1993 and 2003, respectively. At the moment, she serves as the Head and Professor of the Zoology Department at RTM Nagpur University in Nagpur. She has 22 years of research and teaching experience. She has around 60 research papers published in reputable national and international journals, Thomson Bruter (Web of Science and ICI). Her primary areas of study include endocrinology and reproductive physiology.

