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# Toxicological Effects Of Carbendazim On Non – Target Organisms And Its Amelioration By Some Plant Extract

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**Abstract**

Carbendazim is a widely used systemic fungicide belonging to the benzimidazole group, effective in controlling a broad spectrum of fungal diseases in crops. However, its widespread application has raised significant environmental concerns due to its persistence in the environment and its potential toxicity to non-target organisms. Carbendazim can adversely affect various non-target organisms, including aquatic life, soil organisms, and even beneficial insects, mammals etc. In aquatic ecosystems, it is particularly toxic to fish, causing effects such as reproductive failure, developmental abnormalities, and reduced survival rates. Soil organisms like earthworms, which play a crucial role in maintaining soil health, are also negatively impacted, with studies showing reduced growth and reproduction. Additionally, carbendazim can harm beneficial insects like bees, leading to decreased pollination activity, which can have cascading effects on plant biodiversity and crop yields. Experimentally it is observed that it is a potent toxicity on rats also. The toxicity of carbendazim arises from its ability to disrupt the microtubule formation during cell division, which is a critical process in the growth and reproduction of organisms. This mechanism, while effective against fungal pathogens, also affects non-target organisms that share similar cellular processes. To mitigate the adverse effects of carbendazim on non-target organisms, several strategies have been proposed. One approach is the development and use of alternative, eco-friendly fungicides or integrated pest management (IPM) practices that reduce reliance on chemical controls. Additionally, phytoremediation, involving plants that can absorb and degrade carbendazim, has shown promise in reducing environmental residues. Bioremediation using microorganisms that can metabolize carbendazim into less harmful substances is another potential strategy. Strict regulation and monitoring of carbendazim application, coupled with research into its long-term environmental impacts, are also essential to minimize its negative effects on non-target organisms. The main aim of this article is to review the toxicity caused by carbendazim on animals, its residual effects on environment, its effect on animals especially reproductive toxicity, haematological effects, histopathological effects on liver, kidney and gonads and genotoxicity and as chemotherapeutic agents and its amelioration by some mechanisms.

**Key words:** Carbendazim, toxicity, environmental effects, effects on animals, amelioration of effects

## Introduction

Fungi is a plant pathogen and are responsible for wide number of diseases. Most of the diseases are caused by fungi in plants either by killing cells or by causing plant stress. According to Yoon et al. 2013, phytopathogenic fungi have causing extreme losses to crops. Annual wheat and corn yield lost by phytopathogenic fungi are 9% (Matny, 2015) and 30 % (Costa et al., 2019). Fungicide is used to kill these phytopathogenic fungi and reduce these crop losses (Tleuova et al., 2020). Of the 2 million tons per year pesticide used, only 17.5% are used by fungicide administration (De et al., 2014). The carbendazim, a systematic benzimidazole carbamate fungicide is used for protections and treatment for fungal diseases against Ascomycetes, Basidiomycetes and Deuteromycetes (Boudina et al., 2003). According to Xu et al. 2018, due to its high effective use and low cost which makes it suitable globally for application. But it has some negative effects as repeated used makes it unsuitable for field application due to its residual effects and environmental pollution (Chen et al., 2015, Singh et al., 2016). Carbendazim caused environmental pollution and poses potential threats to human health. 2- amino- benzimidazole (2-AB), a degradation product of carbendazim (Kiss and Virag, 2009) is a kind of highly toxic substance which cause inhibition of cell proliferation by blocking the processes of nuclear division (Yenjerba et al., 2009). Though carbendazim is carcinogenic due to its serious toxicity but after banning in several developing countries like Australia, America and Europe (Goodson et al. 2015; Li et al., 2016) but it is still used in China and India (De et al., 2014; Wang et al. 2014). The main objectives of this paper to review the possible risks associated with carbendazim and its amelioration by some mechanisms.

## Residual effects of Carbendazim in environment

Small amount of Carbendazim products was taken by plants and these pesticides resides in the plant body (Singh et al. 2016). After spraying the carbendazim into the leaves, about, 20 – 70 % was absorbed in to the plant body. According to Wang, 2023; carbendazim residue in fruits is 26.4 % and in vegetables ~110 mg $kg^{-1}$. The degradation products are transferred of Carbendazim was transferred to plants through roots, stem or leaves. Repeated use and high dose of carbendazim leads to serious problems for human, livestock, aquatic animals and soil microflora.

## Harmful Effects of Carbendazim on animals

### Carbendazim toxicity on reproduction

Sublethal dose of Carbendazim when administered on rats for eight weeks caused testicular damage, reproductive toxicity and endocrine disruption. Rats exposed to carbendazim showed impaired stages and poor spermatogenesis, reduction in testicular weight, poor sperm motility and altered hormone levels with low sperm count (Zari and Attar, 2011; Gray et al. 1990). Long term effects of carbendazim causes testicular damage, resulting vacuolization of the germinal epithelium, atrophy in the testicular tubules, structural changes in mitochondria and an altered in its structure with expanded endoplasmic reticulum and infertility in male goats. According to Sitarek, 2001, a sublethal dose of Carbendazim and its derivatives causes abnormal sperm head development, germ cell death, pathological changes in Leydig cells. In seminiferous tubules the toxicity caused by carbendazim is oxidative stress, which will not cause reproductive harm but alters foetal embryological health at a dose of 160 ma/kg over a period of 6 to 15 days in female rats. As it causes toxicity in mother, resulting in foetal mental growth retardation, congenital defects and embryonic lethality, umbilical hernias, absent or short tails, skeletal system changes, poor development, delayed mental mental, kidney and other body organ disorders (Organization WHO 2019). Metabolities of carbendazim, 2-aminobenzimidazole, are readily bio-transformable and have

low toxicity in mammals with LD50 values of more than 2000 to 15000 mg/Kg, depending on animal and type of exposure. Carbendazim and its metabolites are readily bio-transformable and have low toxicity in mammals with LD 50 values of more than 2000 to 15000 mg/Kg. A carbendazim dose of 300 mg/Kg causes weight loss and poor nutrition in mothers. Biomolecules such as glucose, cholesterol, protein and creatinine, triglycerides decrease different kinds of hormones such as progesterone and estradiol which cause live foetal birth rate, changes in visceral organs and skeletal deformities (Farag et al. 2011). Different concentration of carbendazim administered at sub-chronically to rats for eighty days before began, concentration of carbendazim 100 and 200 mg/kg were observed cause lower fertility, testicular weight, sperm motility, sperm count. As a result of which Luteinizing hormone decreases but no effects on follicle stimulating hormone and testosterone. According to Yu et al. 2009 atrophy of testicular tubules, stimulation of germ cells and decrease of germ cells.

### Hematological alterations of carbendazim

After administration of carbendazim in male rat when exposed to carbendazim at the rate of 200 mg/kg for one month causes decrease in the levels of haemoglobin, erythrocytes, haematocrit (Hct), plasma proteins and liver proteins and increase in leukocyte count, triglycerides, liver glycogen, total lipids, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (AST) and alanine aminotransferase (ALT) (Zari et al. 2011). Carbendazim when applied @ 50mg/kg to male Wistar rats for nine days causes development of oxidative stress and nitrogen and creatinine (Mirzaei et al. 2015). According to Jacobsen et al. 2004 when carbendazim administered at dose of 450 ppm and 16 mg/kg body weight daily for 28 days resulted in a decrease in red blood cells (RBC) and white blood cells (WBC). When Carbendazim administered in minute doses in male rats and blood samples were collected after 6 hrs showed alteration of different haematological parameters such as erythrocytes, leukocytes, neutrophils, haemoglobin, serum chemical parameters such as AST, Alt, creatinine and cholesterol and liver chemical parameters AST, ALT, creatinine and cholesterol and malondialdehyde (MDA) and histopathological parameters (Muthuviveganandavel et al. 2008).

### Histopathological alterations in kidney, liver and gonads

Histopathological changes are observed when carbendazim was applied for 15 weeks @ 300 and 600 mg/kg showed changes in liver and kidney tissues i.e. Kupffer cell proliferation, portal vein congestion, infiltration in mononuclear cells, sinusoid enlargement and hydrophobic degeneration. In the kidney fibrosis was observed (Selmano et al. 2001). In the kidney highest type of fibrosis was observed after administration of carbendazim (Selmano et al. 2001). Structural changes of renal tissue, such as tubular degeneration, congestion, etc are observed after administration of carbendazim at the rate of 50, 100 and 200 mg/kg for 14 days, which cause changes of histopathological structure in liver and kidney, biochemical changes in the blood parameters, oxidative stress and impairment of liver and kidney function (Pacheco et al. 2012, Salihu et al. 2016; Yu et al. 2009). Several liver morphology has been changed due to exposure of carbendazim such as haemorrhage, dialation and congestion of blood vessels, enlargement of sinusoids, disorganization of hepatic cords and vacuole formation, in the kidney, several changes observed which are damage to cortical and medullary tissues, changes in normal renal corpuscles, glomerulus and Bowman's capsule and in testes changes that are occurred are impairment of spermatogenesis, testicular weight, and testicular morphology (Zari et al. 2011, Rui et al. 2013). Carbendazim is most used fungicide in agriculture and not recommended in the United States of America (USA), most

European countries, and Australia due its acute and chronic effects and persistent nature (Cybulski et al. 1983).

## Genotoxicity by Carbendazim

Carbendazim shows genotoxicity in invitro and in vivo studies. Studies reveal those in vitro concentrations of carbendazim 3.2 to 4.3 and 3.8 to 4.1 µM respectively cause chromosomal aneuploidy in cultured human lymphocytes by fluorescence in situ hybridization (Bentley et al. 2000). Application of carbendazim at 97 % purity in mice as single oral dose of 500 to 1000 mg /kg body weight over 24 to 48 hours of exposure increase in micronuclei observed in intestinal crypts but in signification results was observed in bone marrow and polychromatic erythrocytes for the same dose at irregular intervals (Vanhauwaert, 2001). According to Winder et al. 2001, exposure to carbendazim 100 µM has no effects on tubulin structure and microtubular protein structure (MAPs) and it can play important role in binding of guanosine triphosphate (GTP) to tubulin. During cell division, α and β – tubulin present in heterodimers and play important role in cell division and chromosome segregation (Davidse L.C. 1986). Carbendazim affects normal cell structure, metabolic and physiological processes, cell division and enzymatic activities. In case of Zebra fishes, when carbendazim is applied in sublethal concentration for 96 hrs of exposure, it showed delayed development, dysfunction, pericardial edema, decrease in heart rate, changes in biochemical measurement, changes in locomotor behaviour (Gray et al. 1990). Genotoxicity of carbendazim in a dose range of 125 to 2000 ma/Kg in rats, suggested that it affects cytokinesis and karyokinesis and also cause polychromophilic with pyknotic nuclei, constriction of micronucleated polychromatic (PCE) and normochromatic erythrocytes (NCE) in mouse bone marrow (Ilyushina, 2020).

## Effects of carbendazim on Environment

Carbendazim, persistent fungicide, have half life of 12 months. So, samples are persistent on plant products, soil and water (Kiss and Virág; 2009). Due to its application changes have been observed in soil structure and microbial population and as well as human health. Carbendazim not only pollute target plant but also pollute non target plants also and pollute soil structure for long term because its residues are found to be present in soil for 6 months to 12 years (Ribeiro et al. 2011). By Lysimeter investigation using $C^{14}$ labeled on barley crop when it is applied with carbendazim, it was observed that degradation of carbendazim is more in first phase for four sessions. 33% carbendazim is attached to soil bound particle and in the roots of barley. It could cause toxicity in the environment and retained in the soil if repeatedly applied (Li et al. 2017). Above the recommended quantity, carbendazim is very dangerous, hazardous, decrease in nutrients, foliar pigments and dry weights. Application of carbendazim should be used in control limit to reduce adverse environmental and physiological effects (Xu et al. 2018). In apiculture system, when carbendazim was applied it was observed that carbendazim doses are more in pollens as compared than honey and Royal Jelly (Li et al. 2017). In China effects of carbendazim application is less than in Japan and US (0.01 mg/kg in more than 18,000 samples; Xu et al. 2018). In agriculture, when carbendazim is used it causes long terminal (LTR) retrotransposons polyphorphism, genomic template stability (GTS) and DNA damage. Retrotransposons polymorphism is common in all carbendazim doses, increased phenomenon of DNA damage and decreased genomic template stability. Carbendazim affect both target and non-target organism (Yildrim et al. 2020).

**Promising organic chemotherapeutic agents against Carbendazim toxicity**

Carbendazim is a potent pollutant that causes immense effects on gonads and causes histopathological, hematological and biochemical changes in rats @ 200 mg/kg. Olive leaf extracts lessen the harmful effects of carbendazim in this case (Ribeiro et al. 2011). Carbendazim in combination with licorice (*Glycyrrhiza glabra*) extract histomorphological and histological changes in rats. Licorice extract supplementation cause decreased MDA levels and increased superoxide dismutase (SOD) and catalase (CAT) activity. Licorice extract reduce the testicular toxicity of carbendazim. This happens due to antioxidant properties of one or more of its components (Sakr and Shalaby, 2014). Application of carbendazim on animals also shows adverse effects, but fenugreek administration leads to significant decrease in MDA levels and increase in SOD and CAT activity. Antioxidant properties of fenugreek leaf also help to reduce the adverse effects of carbendazim on testes (Lamfon, 2012). According to Mahboub et al. 2013 *Gingo biloba* extract give good result against carbendazim induced hepatotoxicity by improving liver condition by decreasing AST, ALT level, reducing cellular health and oxidative stress markers. *Guercus brantii* (internal layer called jaft) give effective results when it applied to Wister mice male against carbendazim administration (Mirzaei et al. 2015). 6-Gingerol-rich fraction (6-GRF) obtained from ginger (*Zingiber officinale*) give better results against carbendazim application. It reduces hepatotoxicity and oxidative stress. It also improves liver and kidney health by improving oxidative health of cells and tissues (Salihu et al. 2016). Carbendazim causes hepatorenal toxicity in female mice. *Nigella sativa* oil (NSO) plays important role to reduce its toxicity by improving blood profile for macrocytic hypochromic anemia, white blood cell count, normalization of lymphocyte, eosinophils and neutrophils and by improving liver enzymes such as micronuclei abundance and recovers antioxidant activity (Hashem, 2018). Quercetin, provides better result when it was intragastrically injected into the testis against carbendazim. Quercetin is good as it is effective in maintaining testosterone levels, production of proinflammatory cytokines, increasing cyclic guanine monophosphate (cGMP) levels, reducing oxidative stress and give better result in reproductive markers (Zaid et al. 2018). *Nigella sativa* and *Foeniculum vulgar*, both of them provide good result against carbendazim toxicity in mice as they have antioxidant properties which plays important role in improving chemical composition of blood and alteration in haematological parameters (Alghamdi, 2020). Supplementation of vitamin C, also have antioxidant property which help them to combat fight against carbendazim toxicity in male rats and female chickens (Kiran, 2022; Lalhriatpuia, 2021). Banana peels give good result when it applies against carbendazim toxicity in rats. It improves performance in liver and kidney, lipid profile and histopathological alterations (Abdel – Rahman et al. 2022).

**Conclusion**

Carbendazim is a widely used systemic fungicide known for its effectiveness in controlling a broad spectrum of fungal diseases in crops. However, its use raises significant concerns regarding its adverse effects on non-target organisms and ecosystems. Carbendazim has been found to be toxic to aquatic life, beneficial insects like bees, and soil microorganisms, potentially leading to disruptions in ecological balance and biodiversity loss. Moreover, its persistence in the environment can result in long-term contamination of soil and water bodies.

To mitigate these adverse effects, several remedies have been proposed. These include the development and adoption of more sustainable agricultural practices, such as integrated pest management (IPM), which minimizes the use of chemical pesticides. Biodegradable alternatives to carbendazim, such as biopesticides, are being researched and promoted as safer options.

Additionally, stricter regulations on the use of carbendazim, including better monitoring and enforcement, can help reduce its environmental impact.

Looking to the future, the focus should be on developing innovative approaches to pest and disease management that are both effective and environmentally friendly. Research into the development of new fungicides with lower toxicity profiles, along with the enhancement of crop resistance through genetic and biotechnological means, offers promising avenues. As the agricultural sector moves towards more sustainable practices, the reliance on harmful chemicals like carbendazim is expected to decrease, paving the way for a more balanced coexistence between agricultural productivity and environmental health.

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