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# Hematological and Biochemical Alterations Induced by Two Products from *Metarhizium anisopliae* after Oral Administration in Male and Female Albino Rats

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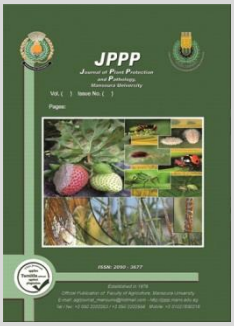


## ABSTRACT

Background: Humans and ecosystems are being harmed by the accumulation of synthetic pesticides in the environment. As a result, the use of bio-pesticides as an alternative to conventional pesticides has increased for control pests. Purpose: The investigation of both male and female rats' physiological status characteristics in relation to a single oral dose toxicity of *Metarhizium anisopliae*. Material and Methods: The local isolate of *M. anisopliae* (AUMC 5130)'s metabolic crude (*Ma*C) and wettable powder formulation (*Ma*F) were evaluated on Sprague Dawley male and female rats. Results: In either of the treated groups, there was no indication of a fatality or toxic effects. The results indicated that there were highly significant increase leucocyte and total erythrocyte counts of male and female treated with *Ma*F and *Ma*C, respectively, compared with control. Also, significant, and insignificant increase in male and female platelet count (Plt) treated with *Ma*F and *Ma*C, respectively. Significant, insignificant, and highly significant increase in male and female ALT, AST, and ALP, respectively, treated with both products (*Ma*F and *Ma*C) of the tested fungus. While lipid profile (T. cholesterol, HDL, LDL and VLDL), levels were decrease in both male and female rats treated with both *Ma*C and *Ma*F compared with control. There have been observed physiological changes in the body weight gain and tissue somatic index of control and all treated animals. When used as bio-insecticides, *Ma*F and *Ma*C products had the opposite effect on body weight gain in rats - a considerable increase - when compared to control groups.

***Keywords:*** Toxicity, Bio-insecticide, *Metarhizium anisopliae*, rats.

## INTRODUCTION

*Metarhizium anisopliae* is a type of fungus that is commonly used as a biological control agent for many years to combat a variety of insect pests, including insects and mites. It acts by infecting and killing the pest, and can be applied in different formulations, such as a spray, bait, or dust. By using *M. anisopliae* in pest control, it is possible to reduce the need for chemical pesticides, which can be harmful to the environment and to human health (Wu *et al*., 2019; Hajek and Leger, 2020; Gao *et al*., 2021; and Zhou *et al*., 2021). The use of *M. anisopliae* as a bio-pesticide has significantly increased in recent years as its effectiveness, low environmental impact, and ability to control pests that are resistant to conventional pesticides (Zhang *et al*., 2021). *M. anisopliae* was effective controlling agent the Asian citrus psyllid *Diaphorina citri* (Yang *et al*., 2021), while another study demonstrated its potential to control the cotton whitefly, *Bemisia tabaci* when used in combination with insecticides (Wang *et al*., 2021). There are several studies suggest that *M. anisopliae* is an effective agent against *Spodoptera littoralis* and Onion Thrips *(Thrips tabaci)* and should be applied in integrated pest management (IPM) as environmentally friendly alternative (Zhang *et al*., 2021; El-Saadany *et al.* 2022). On the other hand, there are little recent studies on determination of biosafety and toxicity of entomopathogenic fungi on mammals and environmental systems such as Ali *et al.* 2022; and Farag, *et al.*, 2022, so, it is important to continue evaluating the safety of *M. anisopliae* and its effects on different parameters to ensure its safe use in pest control. The purpose of this study is to determine orally $LD_{50}$ and biosafety of *M. anisopliae* (AUMC 5130) local strain as metabolic crude (*Ma*C) and formulation (MaF) in rats, both male and female.

## MATERIALS AND METHODS

**The experimental Bio-insecticide:**

*Metarhizium anisopliae* (AUMC 5130), an entomopathogenic fungus, was used in the recent study as crude toxin (*Ma*C) and formulation (*Ma*F, BioMeta, 2.5% WP, $1 \times 10^8$ Conidia or colony forming units, CFU/ml) and obtained from Bio-insecticide Production Unit (BIPU), PPRI, ARC. The formulation used is under registration.

**Fungal culture**

M. anisopliae (AUMC 5130) was identified in the Mycological Centre at the Faculty of Science at Assiut University after being isolated from Hypera bunneipennis in the BIPU-PPRI (Ali and Moharram, 2014). On Czapek-dox agar (CZA), this isolate was grown for 15 days at a

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temperature of 25 1°C and 70% relative humidity (RH) (Ali et al. 2022).

**Crude extract preparation**

Czapek-dox liquid media was adjusted to a concentration of $1x10^8$ conidia/ml in flasks (100 ml). The flasks were incubated for 5 days at 27 1 °C in dark in incubator shaker (150 rpm), producing the Blastospores stage (primary inoculation) (Valencia *et al*., 2011 and Ali *et al*. 2022). Prior to the experiment, the vitality of the fungus was determined.

**Mass production of conidia and formulation**

Boiled rice was autoclaved for 20 min at 121°C in Erlenmeyer flasks (1000 ml). The flasks were cultured for two to three weeks in the dark at 25 ± 1°C after being inoculated with 1 ml of conidia suspension ($10^8$conidia/ml). (Posada-Flórez, 2008). Spores were sorted using sieves after growing them and letting them dry in cardboard bags at room temperature for 15 days. To produce the wettable powder (WP) formula, the spores were added with the powdered additives. One gram of wettable powder (2.5% WP) formula contains to $1 \times 10^8$ conidia or CFU's (Ali, 2016).

**Experimental design**

Thirty adult male and female (nulliparous and non-pregnant) *Rattus norvegicus albinus* Sprague Dawley (SD) rats were provided by the Egyptian Company for Biological Products and Vaccines (Helwan Farm). The animals (males and females) were 6 – 8 weeks old and weighed 180 ± 20 g each. They were acclimated for two weeks under controlled laboratory conditions (12:12 D/L), 25 ± 3°C, 40–70% RH, with unrestricted access to food and water. The test animals were split into two major groups: the first group was used to calculate the oral $LD_{50}$ of two *M. anisopliae* (AUMC 5130) compounds, *Ma*C and *Ma*F, and the second group was utilized to perform biosafety studies following single acute oral exposure.

**Determination of oral $LD_{50}$**

The oral $LD_{50}$ was estimated according to the Organization for Economic Cooperation and Development protocol No. 425 (OECD, 2008). We noted when toxicological symptoms started to appear and how long they lasted in the treated animals. For 21 days, the rats that made it through were observed every day (more details Ali *et al.* 2022 and Farag, *et al.*, 2022). The acute oral $LD_{50}$ values were then determined.

**Acute oral toxicity study**

According to USEPA (1996), the biosafety investigation was carried out after estimating the acute oral $LD_{50}$ value. Five rats/each gender were gavaged with a single dosage (= $LD_{50}$ values) of *Ma*C (0.5 ml/100 g BW) and 1ml *Ma*F (containing $1.1 \times 10^{10}$ conidia /100 g BW) for each of the two Ma products. The treated animals were kept under observation for 21 days. Every day, the body weights of the rats that survived were observed. After the testing periods, the animals were weighed, killed, and dissected. Several vital organs (liver, kidney, brain, spleen, heart, and lung) were carefully removed from both control and treatment animals, cleaned right away with physiological saline (0.9% NaCl), then dried and weighed individually (absolute organ weight). The tissue somatic index (the organ body weight ratio) or relative organ weights (Stanley *et al.* 2005; Nelli *et al.* 2006) was calculated. Mansour *et al.* (2008) provided the formula used to estimate the percentage of changes in the body weight.

**Collection of blood samples**

At the end of the observation period, blood was drawn from the retro-orbital plexus and placed into a tube specifically designed (commercially available) and EDTA-treated for haematological analysis (Complete blood picture, CBC). The tube was filled to the 1-ml level and thoroughly shook several times. Additionally, additional blood samples from each animal were gathered and placed in centrifuge tubes that were clean, dry, and non-heparinized (Schermer, 1967). The serum was obtained by centrifuging the blood samples at 3600 rpm for 15 minutes after allowing them to clot at room temperature for approximately 20 minutes. Until the biochemical analysis was completed, the supernatants (serum) were maintained at -40°C.

**Hematological examination**

The Auto Haematology Analyzer (Countender 20+, SFRI SAS, France) carried out haematological analysis using Theml et al. (2004)'s haematological method. Measurements are provided for the haematological profile. The haematological profile includes measurements for haemoglobin (Hgb), haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), leucogram (white blood cell, WBC), and differentiation of leukocyte counts (DLC). Values for the erythrogram indices were determined using standard formulas. Using recognized formulas of Schalm et al., (1975), values for the erythrogram indices were calculated.

**Biochemical analysis**

The clinico-biomarkers for liver and kidney functions as well as lipid profiles in serum were determined using commercial diagnostic kits. Alkaline phosphatase (ALP) and transaminase (AST and ALT) activities were measured in accordance with Reitman and Frankel (1957) and Roy (1970), respectively. Total protein (TP) and albumin concentrations (Alb) were measured, according to (Bradford, 1976; Doumas *et al*., 1971). The urea level was determined using the method of (Fawcett and Soctt, 1960), whereas the kinetic method of Siest *et al*., (1985) using to determine the creatinine level. The lipid profiles which include levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol, were measured using a spectrophotometer (Allian *et al*., 1974; Buccolo and David, 1973; Friedwald *et al*., 1972). Using Friedewald's equation, it is possible to determine the concentration of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) from the triglycerides. The concentration of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) can be calculated using Friedewald's equation.

**Ethical statement**

The ethical practies and guidelines applied in this work were approved by Zagazig University - Institutional Animal Care and Use Committee (ZU-IACUC) with reference number (ZU-IACUC/2/F/156/2020).

**Statistical analysis**

The oral $LD_{50}$ values of *M. anisopliae* at both products (*Ma*C and *Ma*F) were calculated by using the software AOT425StatPgm, or the "Acute Oral Toxicity (Guideline 425) Statistical Program,". Any percentage-based data were converted into angular transformation

values (arcsin percent) data for the biosafety acute oral toxicity study to conduct the analysis. The data, which were presented as means with standard errors (M ± S.E.), were analyzed using IBM's SPSS for Windows version 25 programme, Chicago, USA. The ANOVA one-way test and Duncan multiple tests were used to evaluate the differences between the treatment groups. The differences between the treatment groups were assessed using the ANOVA one-way test followed by the Duncan multiple tests.

## RESULTS and DISCUSSION

**Acute oral $LD_{50}$ study**

These findings demonstrated that the oral $LD_{50}$ values of *M. anisopliae* in male and female rats were larger than 5000 mg/kg BW for *Ma*F and greater than $1.1 \times 10^{10}$ CFU for *Ma*C products.

One study, for instance, discovered that the orally acute $LD_{50}$ of *M. anisopliae* in rats was greater than 5,000 mg/kg body weight and another revealed that the $LD_{50}$ value of 7,998.3 mg/kg body weight for male rats and 8,427.0 mg/kg body weight for female rats (El-Shenawy *et al*., 2020; Adelabu *et al*., 2021 and Zhang *et al*., 2021). Also, some scientist studied the biosafety of *Beauveria bassiana* (AUMC 9896) as entomopathogenic fungi (EPF) on female and male rats. They reported that the acute oral $LD_{50}$ more than 5000 mg/ kg bw and > 1.1 x $10^{10}$ conidia/kg bw with metabolic crude (MC) and formulation (2.5% WP) products respectively at female and male rats and there were no evidence of death or toxic symptoms in all treated animals (Ali *et al.* 2022 and Farag, *et al.*, 2022).

**Acute oral toxicity study**

**Hematological studies**

The findings, which are summarized in (Tables 1 and 2), revealed that oral administration of both the crude and formulated forms of *M. anisopliae* had a substantial impact on several hematological parameters in male rats. In general, it was noticed that when male rats were treated with $LD_{50}$ of the formulated of *M. anisopliae*, some hematological parameters (hemoglobin, red blood cells, platelets, and white blood cells) were significantly increased, while these hematological parameters were significantly decreased when male rats were treated with $LD_{50}$ of the tested fungus crude compared to control. Regarding female rats that administered with $LC_{50}$ dose of *M. anisopliae* crude and formulation, it was found that the hematological parameters, particularly hemoglobin, red blood cells, and white blood cells, were significantly increased in comparison to control, whereas platelets were significantly decreased.

In male rats, RBC and WBC values were increased significantly when treated with both *Ma*F (WP formulation) and *Ma*C (crude), respectively, however MCH values significantly decreased in all *M. anisopliae* product-treated animals. Females treated with the *Ma*C had considerably higher differential leucocyte counts (DLC) in lymphocytes, monocytes, eosinophils, and neutrophils. Otherwise, no appreciable differences between treatment groups and control group females in Hgb, PCV, MCV, and MCHC were found.

It's worth noting that the dosage and duration of exposure to *M. anisopliae* may vary in different studies, which may account for some of the differences in the results. Additionally, the mode of administration (oral, dermal, etc.) may also affect the hematological parameters. Both male and female rats were treated with a single oral dose of *M. anisopliae*. The hematological parameters such as RBC count, WBC count, Hb concentration, Hct, MCV, MCH, and platelet count were determined. The results indicated that there were not any significant effects on these hematological parameters in both gender (Barros *et al*., 2018). A single oral dose of *M. anisopliae* in both male and female rats resulted in a significant increase in the WBC count, as well as a decrease in the RBC count, Hb concentration, and Hct. (Zhang *et al*., 2021). They suggested that the changes in hematological parameters may be due to the immunomodulatory effects of *M. anisopliae*.

Insignificant changes in hemoglobin, hematocrit, RBCs, WBCs, or platelets in male rats that orally administered with *M. anisopliae* at doses of $2 \times 10^7$, $2 \times 10^8$, and $2 \times 10^9$ conidia/kg body weight for 28 consecutive days.

**Table 1. Influencing Erythrogram and platelet after a single oral dose of *M. anisopliae* in male and female rats.**

| Parameter | Sex | Treatment | | |
|---|---|---|---|---|
| | | | *Ma* | |
| | | Cont. | Crude (*Ma*C) | Form. (*Ma*F) |
| Hgb (g/dl) | Male | 14.62 ± 0.1020 | 14.40 ± 0.1975 | 14.83 ± 0.1592 |
| | Female | 14.2 ± 0.2191 | 14.9 ± 0.3050 | 14.27 ± 0.2244 |
| Hct (%) | Male | 38.29 ± 0.1453 | 38.80 ± 0.2909 | 38.57 ± 0.1861 |
| | Female | 39.10 ± 0.5013 | 39.21 ± 0.4622 | 38.59 ± 0.3023 |
| RBCs (X $10^6$/µl) | Male | 6.492 ± 0.0806$^a$ | 6.410 ± 0.0879$^a$ | 6.732 ± 0.0576$^b$ |
| | Female | 6.292 ± 0.0224$^a$ | 6.522 ± 0.0712$^b$ | 6.348 ± 0.0589$^a$ |
| MCV (fl/cell) | Male | 59.22 ± 1.084 | 61.03 ± 0.2244 | 57.77 ± 0.5695 |
| | Female | 63.18 ± 1.139$^b$ | 61.23 ± 0.6053$^{ab}$ | 59.83 ± 0.2106$^a$ |
| MCH (Pg/cell) | Male | 22.52 ± 0.1562$^b$ | 22.47 ± 0.0966$^b$ | 22.03 ± 0.0658$^a$ |
| | Female | 22.58 ± 0.2975 | 22.8 ± 0.2530 | 22.07 ± 0.0183 |
| MCHC (g/dl) | Male | 38.12 ± 0.4609$^b$ | 36.8 ± 0.03162$^a$ | 38.13 ± 0.3526$^b$ |
| | Female | 35.72 ± 0.2035$^a$ | 37.27 ± 0.0658$^b$ | 36.83 ± 0.1560$^b$ |
| RDW (%) | Male | 22.88 ± 0.1393$^b$ | 22.13 ± 0.3335$^a$ | 21.70 ± 0.1064$^a$ |
| | Female | 21.90 ± 0.2225 | 22.21 ± 0.2618 | 21.75 ± 0.1975 |
| Platelet ($10^3$/mm$^3$) | Male | 755.2 ± 36.87$^b$ | 579.3 ± 15.98$^a$ | 794.7 ± 12.74$^b$ |
| | Female | 681.8 ± 33.16 | 599.2 ± 19.02 | 624.8 ± 25.40 |

***Ma* = *Metarhizium anisopliae.***

**Form. = Formulation**

**Data are presented as mean ± SE (n = 5).**

**Values with different superscripts within rows are significantly different according to Duncan test ($P \leq 0.05$).**

**The percentages were transformed into angular transformation values (arcsin $\sqrt{}$; percent).**

**Table 2. Influencing Leucogram after a single oral dose of *M. anisopliae* in male and female rats.**

| Parameters | Sex | Treatments | | |
|---|---|---|---|---|
| | | Cont. | *Ma* Crude (*Ma*C) | *Ma* Form. (*Ma*F) |
| Total WBCs (X $10^3$/µl) | Male | 6.432 ± 0.3218$^a$ | 8.632 ± 0.3864$^b$ | 8.012 ± 0.3917$^b$ |
| | Female | 7.48 ± 0.3774$^a$ | 9.62 ± 0.4128$^b$ | 10.67 ± 0.4913$^b$ |
| Neutrophil (%) | Male | 21.04 ± 1.143 | 23.03 ± 0.5309 | 21.94 ± 0.6803 |
| | Female | 20.22 ± 0.7597$^a$ | 22.22 ± 0.5872$^{ab}$ | 24.04 ± 0.9973$^b$ |
| Lymphocytes (%) | Male | 64.03 ± 1.489 | 62.30 ± 0.9336 | 63.52 ± 1.182 |
| | Female | 65.72 ± 1.090$^b$ | 64.42 ± 0.4835$^b$ | 59.80 ± 0.6635$^a$ |
| Monocytes (%) | Male | 11.94 ± 0.6726 | 12.82 ± 0.8511 | 11.44 ± 0.7687 |
| | Female | 10.41 ± 0.7653$^a$ | 10.50 ± 0.2854$^a$ | 14.53 ± 0.5624$^b$ |
| Eosinophils (%) | Male | 8.021 ± 0.6730 | 6.571 ± 0.4370 | 8.021 ± 0.6730 |
| | Female | 7.370 ± 0.4371$^b$ | 5.7392 ± 0.0$^a$ | 8.759 ± 0.3368$^c$ |

***Ma* = *Metarhizium anisopliae.*** **Form. = Formulation**
**Data are presented as mean ± SE (n = 5).**
**Values with different superscripts within rows are significantly different according to Duncan test (P ≤ 0.05).**
**The percentages were transformed into angular transformation values (arcsin √√; percent).**

At the end of the treatment period, they determined hematological parameters, including hemoglobin, hematocrit, RBCs, WBCs, and platelets, in the treated rats and compared them to control group rats that did not receive any treatment. They found insignificant differences in any of the hematological parameters between the control group rats and the rats treated with *M. anisopliae*, suggesting that the fungus did not cause any significant changes in these parameters in male rats when used at subchronic doses (El-Shenawy *et al*., 2020). Also, insignificant effects on hematological parameters in either male or female rats were observed when administered orally with *M. anisopliae* at doses of $1 \times 10^6$, $1 \times 10^7$, and $1 \times 10^8$ conidia/mL for 28 consecutive days (Zhang *et al*., 2021). They evaluated hematological parameters, including hemoglobin, hematocrit, RBCs, WBCs, and platelets, in the treated rats and compared them to control group rats that did not receive any treatment. When administration rats orally with *M. anisopliae* at doses of 0, 1000, 2000, and 4000 mg/kg/day for 90 consecutive days. After the 90-day treatment period, the researchers evaluated hematological and biochemical parameters in the treated rats and compared them to control group rats that did not receive any treatment. There were no significant differences in any of the hematological or biochemical parameters between the control group rats and the rats treated with the tested fungus, suggesting that the fungus did not cause any significant changes in these parameters (Zhang *et al*., 2016; Mishra *et al*., 2018 and Zhang *et al*., 2019). They suggested that *M. anisopliae* is generally safe for use in pest control and is unlikely to cause significant changes in hematological parameters in rats when used at subchronic doses. For example, one study found that *M. anisopliae* did not cause any significant changes in hemoglobin, hematocrit, RBCs, WBCs, or platelets in male rats, while another study reported no significant effects on hematological parameters in either male or female rats (El-Shenawy *et al*., 2020; Adelabu *et al*., 2021 and Zhang *et al*., 2021).

**Clinico-biochemical studies**

As indicated in Table (3) and Fig (1), both types of *M. anisopliae* in the exposed female rats induced lower of the ALP and Glb levels with compared to the control group, while ALP level was increased significantly and Glb level was decreased in male rats treated with $LD_{50}$ of the fungi crude and formulated, respectively. All treated male rats had higher TP and Alb. While in female rats treated with a single dose of both the fungi products *Ma*C and *Ma*F led to decrease and increase in ALT levels, respectively, increase and decrease in AST levels, respectively. On the same trend in male case, total proteins (TP), and albumin (Alb) have increased in female rats treated with the same single dose of the formulations (Fig. 1).

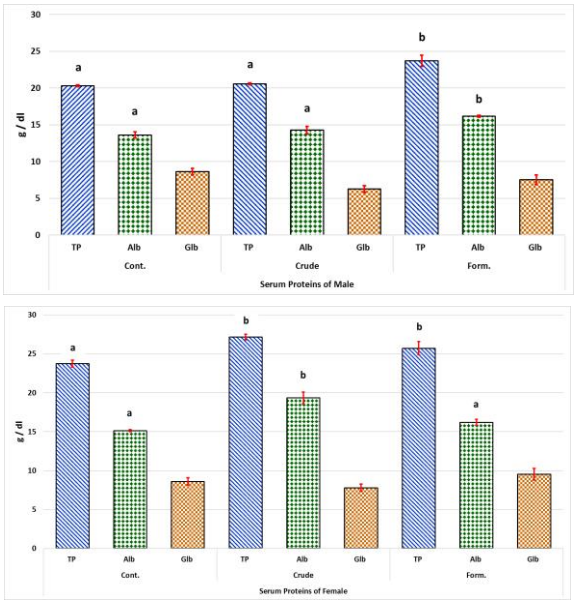



**Fig. 1. Influencing Proteins (g/dl) after a single oral dose of *M. anisopliae* in male and female rats.**

**Table 3. Influencing Liver Functions after a Single Oral Dose of *M. anisopliae* in male and female Rats.**

| Parameters (U/l) | Sex | Treatments | | |
|---|---|---|---|---|
| | | Cont. | Ma Crude (MaC) | Ma Form. (MaF) |
| ALT | Male | 21.68 ± 0.9293$^a$ | 30.876 ± 1.258$^b$ (42.39) | 33.46 ± 1.368$^b$ (54.29) |
| | Female | 32.76 ± 0.7813 | 32.36 ± 1.456 (-1.22) | 33.11 ± 1.575 (1.08) |
| AST | Male | 58.61 ± 2.208 | 64.25 ± 2.649 (9.61) | 61.89 ± 1.739 (5.60) |
| | Female | 63.09 ± 3.163 | 65.5 ± 3.400 (3.82) | 60.34 ± 2.888 (-4.36) |
| ALP | Male | 130.0 ± 6.750$^a$ | 170.2 ± 12.81$^b$ (30.9) | 235.5 ± 9.463$^c$ (81.14) |
| | Female | 116.6 ± 4.521 | 100.1 ± 5.016 (-14.16) | 131.7 ± 8.708 (12.97) |

***Ma* = *Metarhizium anisopliae.*** **Form. = Formulation**
**Data are presented as mean ± SE (n = 5).**
**Values with different superscripts within rows are significantly different according to Duncan test (P ≤ 0.05).**
**Numbers between parentheses refer to "change percentage (%)"ascribed to control**

A single oral dose of *M. anisopliae* was orally administrated to male Sprague-Dawley on serum biochemical parameters were monitored. They found that the treatment with *M. anisopliae* did not cause any significant changes in serum total protein levels or albumin levels, but there was a significant decrease in globulin levels compared to control rats (Ali *et al*., 2019). Similarly, it was found that there were no significant changes in serum total protein levels or albumin levels in Wistar rats treated with a single dose of *M. anisopliae* compared to the control group. However, there was a significant decrease in globulin levels in the treated group, indicating an effect on the immune system (Asadi *et al*., 2020).

The effects of a single oral dose of *M. anisopliae* on biochemical parameters in male rats were investigated. They found that there were no significant changes in liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) compared to control rats. However, there was a significant decrease in total protein levels in the treated rats compared to the control group. They suggested that the decrease in total protein levels may be due to the immunomodulatory effects of *M. anisopliae* (Soleymani *et al*., 2018). In female rats, it was found that the effects of a single oral dose of *M. anisopliae* on biochemical parameters were like male results. They found that there were no significant changes in liver enzymes such as ALT and AST compared to control rats.

There were no significant changes in liver enzyme levels, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), in the treated rats orally with *M. anisopliae anisopliae* at doses of $2 \times 10^7$, $2 \times 10^8$, and $2 \times 10^9$ conidia/kg body weight for 28 consecutive days compared to the control group rats. Similarly, they found no significant changes in electrolyte levels, including sodium, potassium, and chloride, or in kidney function parameters, including creatinine and blood urea nitrogen, in the treated rats compared to the control group rats. These results suggested that *M. anisopliae* did not cause any significant effects on liver or kidney function in male rats when used at subchronic doses (El-Shenawy *et al*., 2020). Also, it was reported significant effects on kidney or liver function in either male or female rats administered orally with *M. anisopliae* at doses of $1 \times 10^6$, $1 \times 10^7$, and $1 \times 10^8$ conidia/mL for 28 consecutive days (Zhang *et al*., 2021). They determined kidney functions (creatinine, blood urea nitrogen) and liver functions (ALT and AST) in the treated rats and compared with control group rats that did not receive any treatment. They found no significant differences in any of the kidney or liver function parameters between the control group rats and the rats treated with *M. anisopliae*, suggesting that the fungus did not cause any significant changes in these parameters in either male or female rats.

According to data on kidney function (Fig. 2), the concentration of urea was significantly lower in female rats treated with MC product than in controls, while it was higher in rats treated with WP formulation. In males, urea levels have increased significantly when treated with WP formulation than fungus crude compared to the untreated control. Creatinine levels in male and female rats treated with single dose of *M. anisopliae* crude and WP formulations, the obtained results indicated highly significant and significant decrease, respectively, compared to male and female control (Fig. 2).

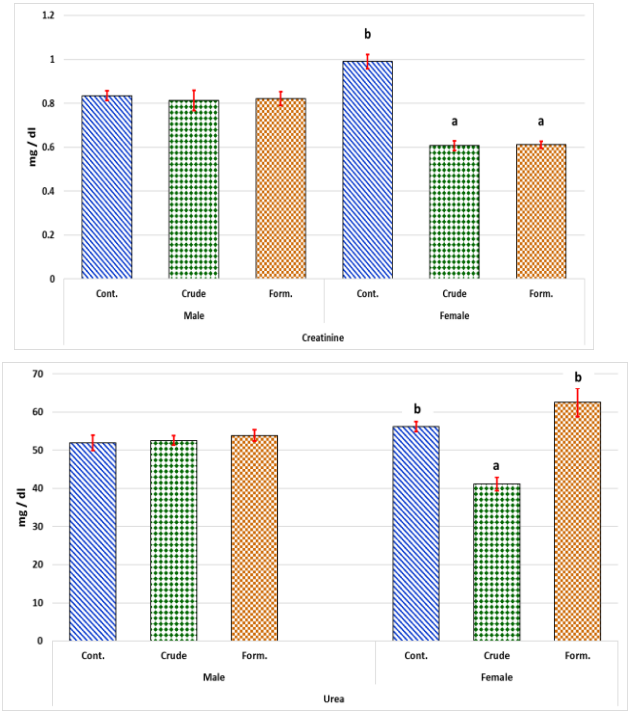



**Fig. 2. Influencing kidney Functions (creatinine and urea) after a single oral dose of *M. anisopliae* in male and female rats.**

However, there was a significant increase in the levels of creatinine and blood urea nitrogen (BUN) in the treated rats compared to the control group (Asadi *et al*., 2020). They suggested that the increase in creatinine and BUN levels may be because of the tested fungus on the renal function.

The lipid profiles analysis in male and female rats treated with *Ma*C and *Ma*F were tabulated in (Table, 4). Male rats administrated with Ma crude, led to increase significantly in total cholesterol, HDL, and LDL, while there were significantly decrease in triglycerides and VLDL. When male treated with *Ma*F, it was found that decrease significantly in all lipid profile parameters (Table 4). Respecting lipid profile parameters in female rats treated with both *Ma*C crude and *Ma*F, it was found that highly significant increase in T. cholesterol and HDL of females treated with Ma WP than Ma crude, whereas there was slightly significant decrease in triglycerides and VLDL of females treated with Ma crude than Ma WP compared to female control.

The oral administration of male rats with *M. anisopliae* may have hypolipidemic effects, led to a significant decrease in serum triglycerides and total cholesterol levels (Shang *et al*., 2019). They suggested that the hypolipidemic effect of *M. anisopliae* may be due to its ability to modulate the gut microbiota.

Total proteins, total cholesterol, triglycerides, HDL, LDL, and VLDL were evaluated in rats orally administrated with *M. anisopliae* or *Beauveria bassiana* at doses of $1 \times 10^7$, $1 \times 10^8$, and $1 \times 10^9$ conidia/kg body weight for 14 consecutive days and compared them to control group rats that did not receive any treatment (Adelabu *et al*., 2021). They found that the tested fungus did not cause any significant changes in total proteins, total cholesterol, triglycerides, HDL, LDL, or VLDL in either male or female

rats. Similarly, the study found no significant changes in these parameters in rats treated with *B. bassiana*. These results suggest that *M. anisopliae* is generally safe for use in pest control and is unlikely to cause significant effects on lipid and protein.

**Table 4. Influencing lipid profile after a single oral dose of *M. anisopliae* in male and female rats.**

| Parameters (mg/dl) | Sex | Treatments | | |
|---|---|---|---|---|
| | | Cont. | Ma | |
| | | | Crude (MaC) | Form. (MaF) |
| T. Cholesterol | Male | 105.7 ± 2.718$^{b}$ | 121.9 ± 1.767$^{c}$ | 98.04 ± 0.5286$^{a}$ |
| | Female | 100.6 ± 2.328$^{a}$ | 101.4 ± 2.059$^{ab}$ | 128.1 ± 3.051$^{b}$ |
| Triglyceride | Male | 71.99 ± 2.201$^{b}$ | 65.95 ± 1.360$^{ab}$ | 69.62 ± 0.7019$^{a}$ |
| | Female | 157.0 ± 9.766$^{b}$ | 104.9 ± 4.319$^{b}$ | 149.8 ± 8.758$^{a}$ |
| HDL | Male | 71.00 ± 2.493$^{ab}$ | 82.37 ± 2.288$^{b}$ | 69.72 ± 0.5016$^{a}$ |
| | Female | 59.56 ± 1.527$^{a}$ | 71.53 ± 1.711$^{b}$ | 72.70 ± 3.603$^{b}$ |
| LDL | Male | 20.34 ± 0.6207$^{b}$ | 26.31 ± 2.125$^{c}$ | 14.39 ± 1.135$^{a}$ |
| | Female | 9.610 ± 0.4293$^{ab}$ | 8.875 ± 0.5163$^{a}$ | 25.39 ± 1.541$^{b}$ |
| VLDL | Male | 14.40 ± 0.4402$^{b}$ | 13.19 ± 0.2719$^{a}$ | 13.92 ± 0.1404$^{ab}$ |
| | Female | 31.41 ± 1.953$^{b}$ | 20.98 ± 0.8637$^{b}$ | 29.96 ± 1.752$^{a}$ |

***Ma* = *Metarhizium anisopliae.*** **Form. = Formulation**
**Data are presented as mean ± SE (n = 5).**
**Values with different superscripts within rows are significantly different according to Duncan test (P ≤ 0.05).**

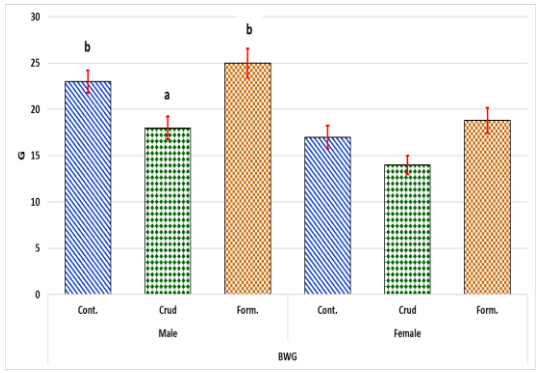
## Body and relative organ weight studies

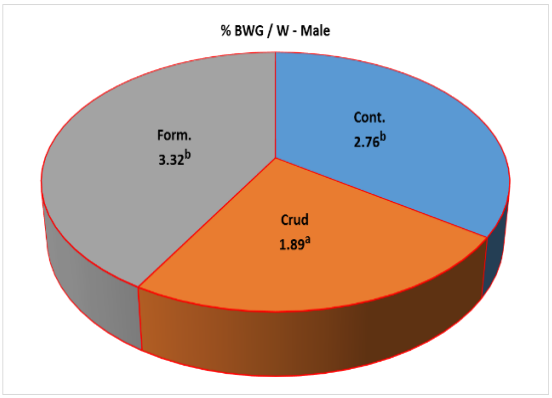
The body weight and tissue somatic index (relative organ weights) of control and treated male and female rats showed physiological changes, as shown in Table (5) and Fig. (3). The results indicated that these products as bioinsecticides had reverse effect on both male and female rats body weight gain exposed to *Ma*C, while there was significant increase in body weight gain of both the gender treated with Ma WP compared to male and female control (Fig. 3).

Respecting tissue somatic index (liver, kidney, spleen, thymus, and bursa of Fabricius) was in rats treated with *M. anisopliae* at doses of 1 × 106, 1 × 107, and 1 × 108 conidia/mL for 28 consecutive days compared them to control group rats that did not receive any treatment. Insignificant changes in tissue somatic index in either male or female rats were observed. Specifically, there were no significant differences in the liver, kidney, spleen, thymus, or bursa of Fabricius weights between the control group rats and the rats treated with *M. anisopliae* (Zhang *et al*., 2021). These results suggest that *M. anisopliae* is generally safe for use in pest control and is unlikely to cause significant effects on tissue somatic index in rats when used at subchronic doses.

The effects on tissue somatic index could vary depending on the dose, duration, and route of administration of *M. anisopliae*, as well as the specific tissues or organs being examined. Repeated exposure over a 90- day period of male rats to *M. anisopliae* led to a decrease in the weight of the adrenal glands and spleen but did not affect the weight of the liver or kidneys (Hou *et al*., 2018). They suggested that the decrease in adrenal gland weight may be related to the immunomodulatory effects of *M. anisopliae*. Adelabu *et al*., (2021) suggested that *M. anisopliae* is generally safe for use in pest control and is unlikely to cause significant effects on tissue somatic index in rats when used at subchronic doses.

The effects of a single oral dose of *M. anisopliae* on body weight gain in male and female rats were evaluated. They found that there was a significant decrease in body weight gain in male rats treated with *M. anisopliae* compared to the control group. Whereas there was no significant difference in body weight gain between the treated and control female rats (Soleymani *et al*., 2018).



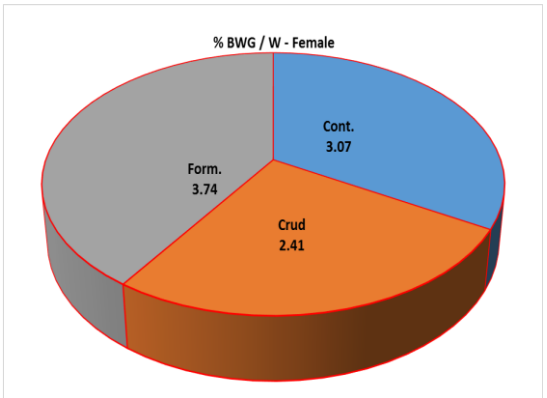




**Fig. 3. Influencing body weight gain after a single oral dose of *Metarhizium anisopliae* in male and female rats.**

***Ma* = *Metarhizium anisopliae.***
**Form. = Formulation**
**Data are presented as mean ± SE (n = 5).**
**Values with different superscripts within rows are significantly different according to Duncan test (P ≤ 0.05).**
**% of weekly body weight gain = [(Final Bw. - Initial Bw) / (Initial Bw X No. of weeks)] x 100**
**The percentages were transformed into angular transformation values (arcsin √ percent).**

**Table 5. Influencing tissue somatic index (g/100gm bw) after a single oral dose of *M. anisopliae* in male and female rats.**

| Parameters | Sex | Treatments | | |
|---|---|---|---|---|
| | | Cont. | Ma | |
| | | | Crude (MaC) | Form. (MaF) |
| Liver | Male | 9.058 ± 0.3695$^{b}$ | 9.446 ± 0.1699$^{a}$ | 9.555 ± 0.0555$^{b}$ |
| | Female | 9.320 ± 0.3809 | 9.960 ± 0.1614 | 10.15 ± 0.1213 |
| Kidney | Male | 4.459 ± 0.1839 | 4.231 ± 0.0911 | 4.285 ± 0.0648 |
| | Female | 4.363 ± 0.0930 | 4.624 ± 0.0651 | 4.993 ± 0.2045 |
| Brain | Male | 4.248 ± 0.0345$^{b}$ | 3.944 ± 0.0825$^{a}$ | 4.373 ± 0.1306$^{b}$ |
| | Female | 4.940 ± 0.0347 | 4.687 ± 0.1472 | 4.998 ± 0.1558 |
| Spleen | Male | 2.894 ± 0.0895 | 2.968 ± 0.1501 | 2.793 ± 0.093 |
| | Female | 2.704 ± 0.0957$^{a}$ | 2.966 ± 0.0261$^{ab}$ | 3.179 ± 0.1591$^{b}$ |
| Heart | Male | 3.210 ± 0.0537 | 2.888 ± 0.1565 | 3.184± 0.0525 |
| | Female | 3.317 ± 0.1034 | 3.483 ± 0.0523 | 3.392 ± 0.1294 |
| Lung | Male | 3.859 ± 0.0358$^{a}$ | 4.038 ± 0.0768$^{a}$ | 4.278 ± 0.0981$^{b}$ |
| | Female | 4.183 ± 0.2915$^{a}$ | 4.560 ± 0.0810$^{ab}$ | 5.160 ± 0.2230$^{b}$ |
| Testes | Male | 5.584 ± 0.2487 | 5.807 ± 0.1691 | 5.873 ± 0.1909 |

**Ma = Metarhizium anisopliae. Form. = Formulation**
**Data are presented as mean ± SE (n = 5).**
**Values with different superscripts within rows are significantly different according to Duncan test (P ≤ 0.05).**
**The percentages were transformed into angular transformation values (arcsin √; percent).**

Also, it was found that a significant decrease in male body weight gain administrated with *M. anisopliae* compared to the control group. They suggested that the effect on body weight gain may be related to the hypolipidemic effect of *M. anisopliae* (Shang *et al*., 2019). Body weight gain in rats orally administrated with *M. anisopliae* or *B. bassiana* for 14 consecutive days was evaluated compared them to control group rats that did not receive any treatment. They found that *M. anisopliae* did not cause any significant changes in body weight gain in either male or female rats. Similarly, the study found no significant changes in body weight gain in rats treated with *B. bassiana* (Adelabu *et al*., 2021). Insignificant changes in body weight gain in either male or female rats orally administered with *M. anisopliae* or *B. bassiana* for 28 consecutive days compared with control group rats. Overall, these studies suggest that *M. anisopliae* is generally safe for use in pest control and is unlikely to cause significant effects on body weight gain in rats when used at subchronic doses (Zhang *et al*., 2021).

Finally, there are some studies suggested that *M. anisopliae* is used safely and non-toxic to humans' health, ecosystem, and other non-target organisms (Guo *et al*., 2021; Kandji & Ekesi, 2021 and Zhang *et al*., 2021). Also, Zhang *et al*., (2018) and Zhang *et al*., (2019) found that the acute and subchronic toxicity studies of *M. anisopliae* on rats and indicated that there were not any significant harmful effects on the rats at the dosages tested. Moreover, Zhang *et al*., (2018) and El-Shenawy *et al*., (2020) reported that the subchronic toxicity of *M. anisopliae* in rats and found no significant changes on hematological and biochemical parameters in either male or female rats.

## CONCLUSION

Generally, the collected data revealed the effects of each product type (*Ma*C and *Ma*F) of *M. anisopliae* (AUMC 5130), a microbial pest control agent (MPCA), on physiological status (CBC, liver and kidney functions, and lipid profile) in male and female albino rats. Additional effects included increases in body weight and the somatic indices of the liver and brain. Complete blood count (CBC) in male and female rats was increased significantly by *M. anisopliae* formulation (*Ma*F) and (*Ma*C), respectively.

We suggested that the changes in body weight or blood parameters might be due to the immunomodulatory effects of *M. anisopliae*. Longer vertebrate pathogenicity/toxicity studies based on local *M. anisopliae* strains should be conducted in the future to preserve ecosystem integrity and reduce hazards to workers, operators, consumers, residents, and bystanders during the production process and application. These studies should be done over a variety of administration routes, time periods, and formulation types.

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# التغيرات الدموية والبيوكيميائية الناتجة عن منتجين من فطر *Metarhizium anisopliae* بعد تناولهما فمياً في ذكور وإناث الفئران البيضاء

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## الملخص

الخلفية: إن تراكم المبيدات الحشرية المصنعة في البيئة ينتج عنه أضرار للإنسان وللنظم البيئية، لذلك ازداد استخدام المبيدات الحيوية كبديل لتلك لمبيدات التقليدية لمكافحة الآفات. الهدف: دراسة المعايير الفسيولوجية لكل من ذكور وإناث الجرذان عند تجريعهم جرعة واحدة فمياً بفطر الـ *Metarhizium anisopliae*. المواد والطرق: تقييم الأمان الحيوى والسمية للمنتج الخام (*Ma*C) ولمستحضر المسحوق القابل للبلل (*Ma*F) لعزلة محلية (AUMC 5130) لفطر *M. anisopliae* على ذكور وإناث الفئران سلالة الـ Sprague Dawley. النتائج: في أي من المجموعات المعاملة، لم يكن هناك ما يشير إلى حدوث وفاة أو آثار سامة. كما أشارت النتائج إلى وجود زيادة معنوية عالية في عدد كريات الدم البيضاء وإجمالي عدد كرات الدم الحمراء للذكور والإناث الذين تم تجريعهم بـ *Ma*F و *Ma*C على التوالي، مقارنة بمجموعة الكنترول. أيضا حدثت زيادة معنوية وغير معنوية في عدد الصفائح الدموية للذكور والإناث (Plt) المعاملة بـ *Ma*F و *Ma*C على التوالي. كما وجدت زيادة ملحوظة وغير معنوية وعالية المعنوية في مستوى إنزيمات ALT و AST و ALP في كلا من الذكور والإناث على التوالي المعاملة بكلا المنتجين للفطر. في حين انخفضت مستويات كلا من صور الدهون والمتمثلة T. cholesterol و HDL و LDL و VLDL في كل من ذكور وإناث الفئران التي تم تجريعها بكل من *Ma*C و *Ma*F مقارنة مع مجموعة الكنترول. أما بالنسبة للتغيرات الفسيولوجية في وزن الجسم والمؤشر الجسدي للأنسجة (الأوزان النسبية للأعضاء) لجميع الحيوانات المعاملة فقد كان لكلا المنتجين *Ma*F و *Ma*C - كمبيدات حشرية حيوية - تأثير عكسي على زيادة وزن الجسم (زيادة معنوية) لكل من ذكور وإناث الفئران عند المقارنة بمجموعات الكنترول.

***الكلمات الدالة:*** سمية، مبيد حيوي*Metarhizium anisopliae*، فئران