World Journal of Pharmacology and Toxicology

Jason, World J Pharmacol Toxicol 2022, 5:2

Commentary Open Access

Toxicology and Safety Measures of *Weissella cibaria* Strain CMU in Animal Toxicity and Genotoxicity

Rachel Jason*

School of Health Sciences, Purdue University, West Lafayette, IN 47907, United States of America

Commentary

Description

W. cibaria CMU is being developed for use in human food and dietary supplements. Results of previous studies indicate that the strain is susceptible to common antibiotics, with the possible exception of kanamycin and vancomycin, but does not transfer resistance of these antibiotics to other bacteria. Genetic analysis confirmed that antibiotic resistance to kanamycin is an intrinsic characteristic of *W. cibaria* and is not unique to *W. cibaria* CMU. Additional studies performed by Kang et al. [1] showed that *W. cibaria* CMU does not harbor virulence genes associated with pathogenic bacteria, does not cause hemolysis, mucin or protein degradation, or platelet aggregation, and does not produce D-lactate or urease (which catalyzes the hydrolysis of urea to ammonia). However, animal toxicity or genotoxicity studies on *W. cibaria* strains have not been conducted previously. Results of the studies described herein add to the database of information that *W. cibaria* CMU will be safe for human consumption.

When administered acutely to rats by gavage up to 5000 mg/kg bw (1.8×10^9 CFU/kg bw), the highest dose administered was well tolerated. This dose was chosen as the highest dose administered in a 14-day range finding and 13-week study in rats. In the 14-day study, changes in MPV of males receiving 2500 and 5000 mg/kg bw/day, NEP in females receiving 1250 and 2500 mg/kg bw/day, and BUN and TG in females receiving 1250 mg/kg bw/day were not considered to be toxicologically relevant due to lack of dose dependency and/or minor nature of the changes [2]. Changes in these variables were not found in rats receiving up to 5000 mg/kg bw (1.8×10^9 CFU/kg bw) *W. cibaria* CMU for ninety days, supporting the conclusion that the findings in the 14-day study were not toxicologically relevant.

The no observed adverse effect level (NOAEL) of the 13-week study is 5000 mg/kg bw/day (1.8×10^9 CFU/kg bw/day), the highest dose administered. In the 13-week study, the most notable effect of administration of the test material was reduced body weight and food consumption of males in the 2500 and 5000 mg/kg bw/day groups. The study investigators did not consider the findings to be adverse because the body weights of the animals were within 10% of the vehicle control group. The 10% criterion is commonly used to determine whether an effect of a test material on body weight is adverse. Changes in a few hematological, coagulation, and clinical chemistry parameters were observed in treated animals; however, the study investigators considered them not to be toxicologically relevant due to lack of dose response-relationship and biologically insignificant degree of change. Regarding the urinalysis, the specific gravity of the male test groups and pH levels of the male and female test groups showed dose-dependent increases. At the 5000 mg/kg bw/dose, the urine volume of males was less than controls. The reason for this is unclear but could be possibly due to decreased water consumption by this group. Because water consumption was not measured, this cannot be confirmed. As noted by the study investigators, no abnormal changes in clinical pathology and histopathology related to the kidney were observed. Values for hematological, coagulation, clinical chemistry and urinalysis parameters reported for the treated groups that exhibited statistically significant changes from controls are also within the range of normal for SD rats as reported by Derelanko [3], lending support to the study investigator's conclusion that the changes observed in treated animals are not adverse. No abnormal gross findings were observed at necropsy, and all histopathological lesions that were observed were considered to be incidental or spontaneous due to similar incidences in control and high dose animals. A few changes in organ weights were observed in treated animals compared to controls but they were not considered to be adverse due to lack of dose–response relationship or corresponding histopathological or clinical chemistry findings.

W. cibaria CMU was not mutagenic in an OECD Guideline 471 bacterial reverse mutation assay which tested concentrations up to the limit concentration of 5000 µg/plate (in the presence and absence of metabolic activation) or clastogenic in an OECD Guideline 473 in vitro chromosome aberration assay in cultured CHO-k1 cells. Both of the assays met the criteria for validity that are required by the OECD. The results of an OECD 474 Guideline micronucleus study in the mouse show that *W. cibaria* CMU is not clastogenic or aneugenic up to 5000 mg/kg bw. Toxicity was not noted in the micronucleus study- there was no effect of the test substance on body weight or PCE/PCE + NCE ratio and no abnormal clinical signs were noted [4]. However, the study is valid and fit for purpose because the assay was sensitive enough to detect micro nucleated PCE (as indicated by the positive control response), and the highest dose of *W. cibaria* CMU administered was the same dose evaluated for safety in rats. Further, the 5000 mg/kg bw dose is higher than the limit dose of 2000 mg/kg bw recommended by the OECD.

In conclusion, the results of the studies described in this manuscript show that oral administration of up to 5000 mg/kg bw/day (1.8×10^9 CFU/kg bw/day) *W. cibaria* CMU is safe in rats and suggest that the strain could be safely consumed by humans. Furthermore, *W. cibaria* CMU is non-genotoxic as shown by the negative results of in vitro bacterial reverse mutation and CHO-k1 cell chromosome aberration studies and the in vivo micronucleus study in mice [5]. This study is the first study examining the potential of a *W. cibaria* strain to cause genetic toxicity and sub chronic toxicity in rats according to OECD guidelines.

***Corresponding author:** Rachel Jason, School of Health Sciences, Purdue University, West Lafayette, IN 47907, United States of America, E-mail: rachel.j@gmail.com

Received: 16-Mar-2022, Manuscript No. wjpt-22-57455; **Editor assigned:** 18-Mar-2022, PreQC No. wjpt-22-57455 (PQ); **Reviewed:** 01-Apr-2022, QC No. wjpt-22-57455; **Revised:** 06-Apr-2022, Manuscript No. wjpt-22-57455 (R); **Published:** 13-Apr-2022, DOI: 10.4172/wjpt.1000153

Citation: Jason R (2022) Toxicology and Safety Measures of *Weissella cibaria* Strain CMU in Animal Toxicity and Genotoxicity. World J Pharmacol Toxicol 5: 153.

Acknowledgement

I would like to acknowledge School of Health Sciences, Purdue University for giving me an opportunity to do research.

Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

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