International Journal of Biotechnology and Microbiology
www.biotechnologyjournals.com
Online ISSN: 2664-7680, Print ISSN: 2664-7672
Received: 22-11-2023, Accepted: 07-12-2023, Published: 23-12-2023
Volume 5, Issue 4, 2023, Page No. 29-33

The effect of Mirabegron on liver activity in adult female rats (Rattus norvegicus) and the vital role of Ganoderma lucidium

Hamid Muhadras Rahil, Waad Sabri Shaher
Department of Life Sciences, College of Science, University of Mosul, Iraq

Abstract
Recent research end eavors have focused on exploring hepatotoxicity resulting from the administration of certain pharmaceutical drugs and antibiotics, which elicit oxidative stress and elevate the production of free radicals. This perturbation leads to the disruption or inhibition of enzymatic and non-enzymatic antioxidant defense mechanisms within the liver. Following a two-month experimental period, the study subjects, i.e., animals, were subjected to anesthesia, and blood specimens were obtained via the ocular sockets for the purpose of assessing various biochemical parameters.
The biochemical analyses encompassed the determination of liver enzyme activities, specifically, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The results derived from comprehensive statistical analysis unequivocally revealed the deleterious impacts of Mirabegron, characterized by a significant elevation in the levels of liver enzymes ALT, AST, and ALP. Notably, this effect was notably prominent at a concentration of 10 mg/kg. However, it is worth noting that ALP displayed a distinct response, exhibiting a decrease that, while discernible, did not attain statistical significance in comparison to the control group.
Conversely, Ganoderma lucidum exhibited a protective influence, manifesting its role in mitigating the aberrant enzyme concentrations, restoring them to their baseline levels akin to those observed in the control group. Alternatively, it effectively attenuated the significant discrepancies when contrasted with the administration of Mirabegron.

Keywords: Pharmaceutical drugs, Mirabegron, Ganoderma, ALT

Introduction

The administration of pharmaceutical drugs often engenders collateral effects that can detrimentally impact various bodily organs (Huang *et al*., 2011) [7]. Amongst the prevalent human maladies, overactive bladder syndrome stands as a commonly encountered condition, characterized by several hallmark symptoms, including urinary urgency and associated urinary tract disorders (Ouslander, 2004) [16].
The primary objective of addressing overactive bladder syndrome is to alleviate the distressing symptoms, with pharmacological intervention predominantly relying on antimuscarinic agents (Chapple *et al*., 2008) [4]. However, longitudinal assessments by Wagg *et al*. (2012) [22] have revealed that despite the efficacy of these agents in a substantial proportion of patients, they are marred by a considerable incidence of adverse effects, notably encompassing dry mouth, constipation, and blurred vision (Sacco *et al*., 2008) [19].
A pivotal pharmacological approach involves the utilization of Mirabegron, employed as an alternative therapeutic strategy for managing overactive bladder syndrome. Clinical investigations have demonstrated the beneficial impact of Mirabegron in ameliorating urinary urgency, with a relatively diminished side-effect profile compared to traditional antimuscarinic medications (Chapple *et al*., 2014). Nonetheless, it is imperative to acknowledge that Mirabegron is not devoid of its own side effects, encompassing ocular disturbances, elevated blood pressure, urinary tract disorders, and arrhythmias (Chaplin & Chapple, 2013) [3].
Consequently, the imperative pursuit centers on mitigating these adverse effects associated with pharmacotherapy, prompting the selection of Ganoderma lucidum, commonly known as reishi mushroom, as a potential modulator of these effects, owing to its composition of bioactive compounds (Paterson, 2006) [17]. Research by Wang and Lin (2000) [23] has underscored the significant hepatoprotective effects of triterpenes found in mushrooms, particularly G. lucidum, against hepatic damage in rodent models. Moreover, the administration of G. lucidum extracts has shown promise in safeguarding rat liver cells from hepatic necrosis, further accentuating its potential role in minimizing drug-induced hepatic injury.

Materials and Methods

1. Experimental Animals

Adult female white rats, aged between 2.5 and 3 months, and weighing between 200-250 grams, were sourced from the animal facility at the College of Veterinary Medicine, University of Mosul. These rats were verified to be in good health. The study was conducted within the animal facility over a duration spanning from February 1, 2022, to December 1, 2022. During this period, the rats received vaccination for two months, from April 1, 2022, to June 1, 2022. The animals were housed in plastic cages equipped with metal mesh covers, with the cage floors layered with sawdust. The sawdust bedding was replenished daily to ensure a clean environment. The animals were maintained under standardized laboratory conditions, encompassing adequate ventilation and a temperature of 25±2°C, following a photoperiod cycle of 12 hours of light and 12 hours of darkness (Salem *et al*., 2011). The rats were provided with a specialized diet designed to meet their nutritional requirements, consisting of 34% wheat, 20% barley, and 1% table salt. Throughout the study, the animals

received continuous care and monitoring until the commencement of the experimental procedures. The experimental cohort consisted of 60 female rats, randomly allocated into 6 groups, each comprising 10 animals.

2. Measurement of Liver Enzyme Activity

Estimation of ALT and AST Enzymes Activity

To assess the activity of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the blood, a commercially available kit, manufactured by Biolabo (France), was employed in accordance with the manufacturer's instructions.

Evaluation of Alkaline Phosphatase (ALP) Enzyme Activity

To determine the levels of alkaline phosphatase (ALP) enzyme in the blood, a kit provided by BioLabo (France) was employed, and the methodology was executed in accordance with the manufacturer's guidelines.

Results and Discussion

1. The Effectiveness of Liver Enzymes

1.1 The Effect of Mirabegron on ALT Activity in Female Albino Rats and the Role of G. lucidum

Table 1 illustrates the impact of Mirabegron at a concentration of 5 mg/kg on the activity of alanine aminotransferase (ALT) in adult female white rats. The group administered Mirabegron at a concentration of 10 mg/kg displayed an ALT activity of 23.33 IU/L compared to the control group, while G. lucidum fungus did not exhibit significant differences compared to the control group, with ALT activities of 21 and 20.46 IU/L, respectively.

Statistical analysis, as depicted in Figure 1, revealed a noteworthy increase ($P \leq 0.05$) in ALT enzyme activity for the groups treated with Mirabegron at 5 and 10 mg/kg in comparison to the remaining experimental groups. In the presence of G. lucidum fungus, a protective effect was observed, with no significant differences compared to the control group.

Table 1: Shows the effect of Mirabegron on the activity rate of liver enzymes in female albino rats and the role of G.lucidum fungus

Standards transactions	ALP IU/L	AST IU/L	ALT IU/L
control coefficient	90.66±7.02ab	21.40± 4.08 b	20.03±2.12b
Mirabegron at a concentration of 5 mg/kg	97.00± 13.89a	28.00±0.57a	25.36±1.48a
Mirabegron at a concentration of 10 mg/kg	88.66±31.50ab	23.66±1.52ab	23.33±2.08ab
Ganoderma lucidum mushroom	90.33±5.29 ab	21.60± b 3.14	20.43± b 1.40
Mirabegron at a concentration of 5 mg / kg + G.lucidum fungus	93.33±20.81ab	24.33±3.21ab	21.00±3.00b
Mirabegron at a concentration of 10 mg / kg + G.lucidum fungus	74.33±5.13ab	22.66±1.52b	20.46±1.85b

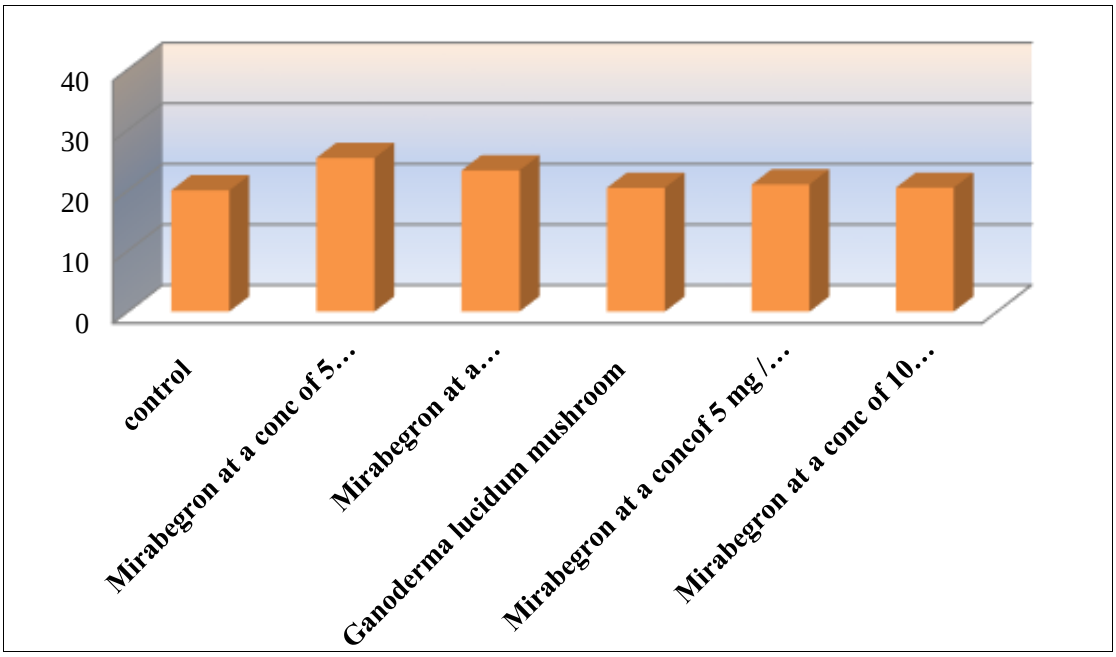

Fig 1: shows the effect of Mirabegron on the rate of activity of the aminotransferase enzyme ALT (IU/L) in the blood serum of female albino rats and the role of G.lucidum fungus after two months of treatment.

1.2 The Effect of Mirabegron on AST Activity in Female Albino Rats and the Role of G. lucidum

Table 1 portrays the influence of Mirabegron at a concentration of 5 mg/kg on aspartate aminotransferase (AST) activity in adult female white rats. Results indicated a substantial increase in AST activity, reaching 28 IU/L compared to the control group's 21.40 IU/L. Meanwhile, the group treated with Mirabegron at 10 mg/kg exhibited an AST activity of 23.66 IU/L, also higher than the control group. However, the presence of G. lucidum fungus did not yield significant differences, with AST activities at 21.60 IU/L in comparison to the control group. The co-administration of G. lucidum with Mirabegron mitigated the activity of AST enzyme, with no significant differences observed at 24.33 and 22.66 IU/L compared to the control group.

Statistical analysis, depicted in Figure 2, highlighted a significant increase (P≤0.05) in AST enzyme activity for the groups treated with Mirabegron at both 5 and 10 mg/kg compared to other experimental groups. In the presence of G. lucidum, the protective effect was evident, with no significant differences compared to the control group.

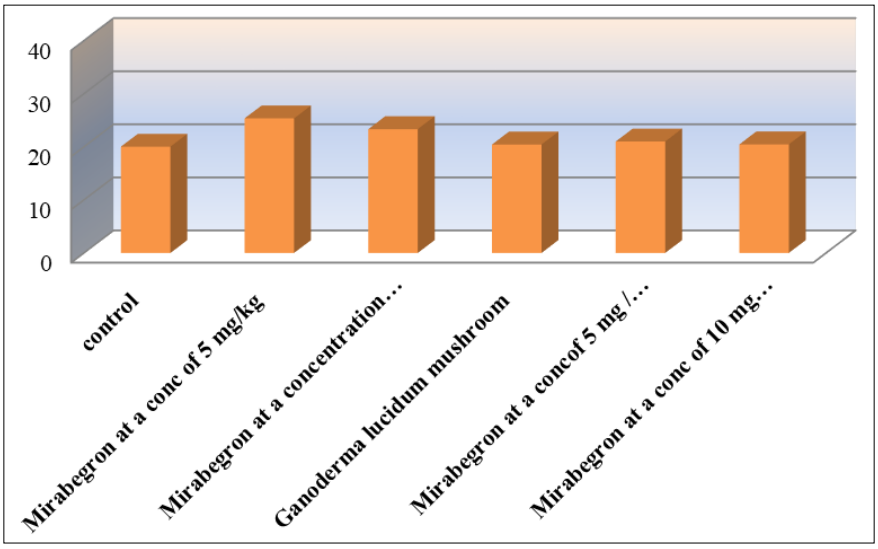

Fig 2: The effect of Mirabegron on the rate of activity of the aminotransferase enzyme AST (IU/L) in the blood serum of female albino rats and the role of G.lucidum fungus after two months of treatment.

1.3 The Effect of Mirabegron on ALP Activity in Female Albino Rats and the Role of G. lucidum

Table 1 outlines the influence of Mirabegron at a concentration of 5 mg/kg on alkaline phosphatase (ALP) activity in adult female white rats. The results showed an increase in ALP activity to 97 IU/L compared to the control group's 90.66 IU/L, while the group treated with Mirabegron at a concentration of 10 mg/kg displayed an ALP activity of 88.66 IU/L compared to the control group. Results for G. lucidum did not indicate significant differences, with ALP activity at 90.33 IU/L compared to the control group. The presence of G. lucidum in the presence of Mirabegron at 5 mg/kg decreased ALP enzyme activity, with no significant differences observed (23.33 and 74.33 IU/L) compared to the control group.

Statistical analysis, presented in Figure 3, revealed a Significant increase (P≤0.05) in the activity of ALT, AST, and ALP enzymes in adult female white rats for groups treated with Mirabegron at both 5 and 10 mg/kg, compared to the control group. Notably, ALP enzyme activity exhibited a decrease at the 10 mg/kg Mirabegron concentration, although not reaching statistical significance. These findings align with studies such as AusPAR (2014) [2] which demonstrated an increase in liver enzyme concentrations during prolonged studies.

In line with this, observations of patients treated with Mirabegron at 50 mg/kg daily indicated elevated liver enzyme activity beyond normal limits in some cases (John & Cunha, 2022) [11]. Furthermore, Schmid & Hovda (2018) [20] reported significant hepatotoxicity and subsequent increases in liver enzymes in dogs subjected to repeated doses of Mirabegron at 8.3 mg/kg within two weeks.

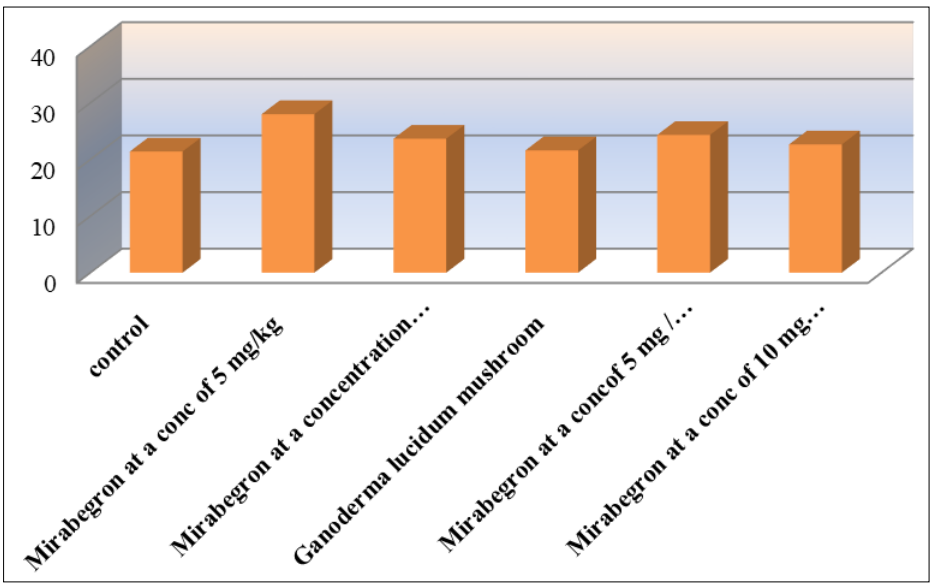

Fig 3: Shows the effect of Mirabegron on the rate of activity of the enzyme alkaline phosphatase ALP (IU/L) in the blood serum of female albino rats and the role of G.lucidum fungus after two months of treatment.

While the current results demonstrated a decrease in ALP enzyme activity when treated with Mirabegron at a concentration of 10 mg/kg, with changes in liver tissue, significant histological alterations occurred. These findings align with studies by Koff *et al*. (2004) [13], suggesting that severe liver damage may hinder the production of enzymes, potentially maintaining some enzyme concentrations within the normal range.

Conversely, some studies, like Elbadr *et al*. (2020) [5], reported that Mirabegron treatment at a concentration of 10 mg/kg led to a significant decrease in liver enzyme activity. Andriulli *et al*. (2001) [1] pointed out that the activity of liver enzymes may have limited clinical value, as increased activity may not always correlate with the severity of tissue damage. Khaddam (2007) [12] highlighted that the absence of elevation in certain enzymes does not necessarily negate the presence of infection.

Studies conducted by Jiang *et al*. (2021) [10] found that G. lucidum mushroom exhibited protective effects against toxicity and tissue damage, including the liver, induced by acrylamide in rats. The results indicated that pre-treatment with the mushroom could prevent damage caused by acrylamide, which led to increased ALT, AST, and ALP activities.

Additionally, Oluba *et al*. (2010) [15] reported that pre-treatment with G. lucidum mushroom reduced the effects of CCl4 poisoning, as it resulted in a non-significant decrease in liver enzymes. The protective effect was attributed to the prevention of enzyme leakage from tissues into the bloodstream. Shi *et al*. (2008) [21] observed that G. lucidum effectively mitigated hepatic damage induced by d-GalN, reducing enzyme activities to normal values.

Furthermore, Zhou *et al*. (2007) [25] suggested that G. lucidum had no effect on increasing serum aspartate aminotransferase enzyme activity, emphasizing its hepatic protective properties against liver damage. Jia *et al*. (2009) [8, 9] attributed G. lucidum to increasing antioxidants and enzyme activity in the blood and liver. This enhancement is attributed to bioactive compounds present in the mushroom, such as flavonoids, polysaccharides, and triterpenoids, which are known for their ability to inhibit free radicals and prevent lipid oxidation. Recent studies have concluded that G. lucidum mushroom extracts contain key constituents, like triterpenoids, which protect the liver from induced injury by inhibiting lipid peroxidation, increasing antioxidant enzyme activity, and preventing apoptotic cell death and immune inflammatory responses (Zhao *et al*., 2019) [24].

Conclusion

In summary, Mirabegron administration led to significant increases in the activity of ALT, AST, and ALP enzymes in the blood of female albino rats, particularly at concentrations of 5 and 10 mg/kg, compared to the control group. However, the protective effects of G. lucidum mushroom were evident, as it mitig.

References

1. Andriulli A, Festa V, Leandro G, Rizzetto M. Usefulness of a liver biopsy in the evaluation of patients with elevated ALT values and serological markers of hepatitis viral infection. Digestive diseases and sciences,2001:46:1409-1415.
2. Aus PAR Betmiga mirabegron Astellas Pharma Australia Pty Ltd PM-2012-01928-3-3 Date of Finalisation,2014:5:74.
3. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, *et al*. Randomized double-blind, activecontrolled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β3-adrenoceptor agonist, in overactive bladder. Eur Urol,2013:63:296–305.
4. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. European urology,2008:54(3):543-562.
5. Elbadr MM, El Badre HM. Hepatoprotective and antiobesity effects of mirabegron, a novel β3-adrenoceptor agonist, on carbon tetrachloride-induced hepatotoxicity in obese rats. Journal of Current Medical Research and Practice,2020:5(3):254.
6. Fischer AW, Cannon B, Nedergaard J. Optimal housing temperatures for mice to mimic the thermal environment of humans: an experimental study. Mol Metab,2018:7:161–170.
7. Huang LC, Wu X, Chen JY. Predicting adverse side effects of drugs. BMC genomics,2011:12(5):1-10.
8. Jia J, Zhang X, Hu YS, Wu Y, Wang QZ, Li NN, *et al*. Evaluation of *In vivo* antioxidant activities of Ganoderma lucidum polysaccharides in STZ-diabetic rats. Food Chemistry,2009:115(1):32-36.
9. Jia J, Zhang X, Hu YS, Wu Y, Wang QZ, Li NN, Dong XC. Evaluation of *In vivo* antioxidant activities of Ganoderma lucidum polysaccharides in STZ-diabetic rats. Food Chemistry,2009:115(1):32-36.
10. Jiang G, Lei A, Chen Y, Yu Q, Xie J, Yang Y, Su D. The protective effects of the Ganoderma atrum polysaccharide against acrylamide-induced inflammation and oxidative damage in rats. Food & function,2021:12(1):397-407.
11. John P. Cunha DO. FACOEP Last updated on RxList: MYRBETRIQ 10/25/2022. https://www.rxlist.com/myrbetriq-drug.htm.
12. Khaddam W. Variations of ALT Serum Levels in Chronic Viral Hepatitis C Patients, Jumada Al-Akhirah 1428, 2007, 4(6).
13. Koff JM, Younossi Z. PRO: Most Patients Should be Treated. Official journal of the American College of Gastroenterology| ACG,2004:99(6):972-973.
14. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet,2003:42:59-98.
15. Oluba OM, Onyeneke EC, Ojieh GC, Idonije BO, Ojiezeh TI. Hepatoprotective potential of aqueous extract of Ganoderma lucidum against carbon tetrachloride intoxication in rats. Der Pharmacia Lettre,2010:2(4):432-439.
16. Ouslander JG. Management of overactive bladder. New England Journal of Medicine,2004:350(8):786-799.
17. Paterson R. Ganoderma: A therapeutic fungal biofactory. Phytochemistry,2006:67(18):1985-2001.
18. Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. Autonomic Neuroscience,2007:133:3-18.
19. Sacco E, Pinto F, Bassi P. Emerging pharmacological targets in overactive bladder therapy: experimental and clinical evidences. International Urogynecology Journal,2008:19:583-598.

20. Schmid RD, Hovda LR. Mirabegron toxicosis in dogs: a retrospective study. Journal of Medical Toxicology,2018:14(2):160-167.
21. Shi Y, Sun J, He H, Guo H, Zhang S. Hepatoprotective effects of Ganoderma lucidum peptides against D-galactosamine-induced liver injury in mice. Journal of Ethnopharmacology,2008:117(3):415-419.
22. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int,2012:110(11):1767-74.
23. Wang SY, Lin HS. Antioxidant activity in fruits and leaves of blackberry, raspberry, and strawberry varies with cultivar and developmental stage. Journal of agricultural and food chemistry,2000:48(2):140-146.
24. Zhao C, Fan J, Liu Y, Guo W, Cao H, Xiao J, Liu B. Hepatoprotective activity of Ganoderma lucidum triterpenoids in alcohol-induced liver injury in mice, an iTRAQ-based proteomic analysis. Food chemistry,2019:271:148-156.
25. Zhou X, Lin J, Yin Y, Zhao J, Sun X, Tang K. Ganodermataceae: natural products and their related pharmacological functions. Am J Chin Med,2007:35(4):559-74.