Pharmacogn J. 2023; 15(1): 189-193
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Inflammatory Thyroid Changes Following Serotonin Receptor Blocking in Experimental Rats

Muthear N Dawood*, Karam A. Aldabbagh[1], Zahraa Alsarraf[2]

ABSTRACT

According to studies, a pathophysiological feature of schizophrenia may be a dysregulation of the inflammatory immune response. Conversely, antipsychotic medications have been found to have an immunosuppressive effect in patients with schizophrenia; however, this has not been consistently observed in different studies. The purpose of the following study is to compare the effects of risperidone with aripiprazole on thyroid function as it relates to inflammatory markers (CRP). This study was based on a randomized controlled trial. A total of thirty rats were recruited for the experiment and were kept in the artificial, and optimal environment. The rats were divided into three groups; each group has an equal number of rats which was 10 rats each. The first group was the control group which received the placebo, in the second group, there were 10 rats too, which was known as the risperidone group. Each rat received 20mg/kg/day through I/V. The third group is known as the aripiprazole group which received the drug from the intravenous route, 10mg/kg//day. In the results, the summarized values represented that all the mean values before and after the treatment remained less than 3.0. From the results and other evidence, it can be said that although the subjects who receive the following results do not require regular or frequent monitoring of thyroid hormones in long-term use and in the use of the drug in higher concentration there must be a check as long term use is associated with hyperthyroidism.

Key words: Thyroid, FT3, FT4, Thyroxine, Tri-iodothyronine, Aripiprazole, Risperidone.

Muthear N Dawood[1],*, Karam A. Aldabbagh[1], Zahraa Alsarraf[2]

[1]College of Pharmacy, University of Mosul, Mosul, IRAQ.

[2]Department of Pharmacy, Al-Hadba University College, Mosul, IRAQ.

Correspondence

Muthear N Dawood

College of Pharmacy, University of Mosul, Mosul, IRAQ.

E-mail: muthear78@uomosul.edu.iq

History

- Submission Date: 29-12-2022;
- Review completed: 26-01-2023;
- Accepted Date: 30-01-2023.

DOI : 10.5530/pj.2023.15.28

Article Available online

http://www.phcogj.com/v15/i6

INTRODUCTION

Bipolar disorder, schizophrenia, and depressive disorder are all common yet serious mental illnesses with potentially negative disability consequences.[1] The cognitive changes observed in these mental conditions are commonly associated with the impairment of cognitive functions. According to research, the developmental trajectory of neuropsychological functioning appears to be independent of diagnosis. Since pharmacological strategies to improve cognitive performance in these disorders, there is still a lack of studies and research which can indicate the biomarkers which are responsible for inducing cognitive impairment and developing cognitively beneficial drugs.[2,3] In the following domain, the studies based on hormones or therapeutic drugs that target the hormonal system is a promising areas of research. Most clinical studies of cognitive enhancers in patients with psychiatric disorders have emphasized medicines that target the hypothalamic-pituitary-adrenal axis.[4]

As indicated in research, clinical and subclinical hypothyroidism is common in patients with resistant depression, with a prevalence of approximately 20%. Given the interrelationship between hypothyroidism and depression, and the cognitive consequences, thyroid hormones may improve cognitive function in both disorders.[5,6] Due to a lack of research, data on the effect of thyroid abnormalities on cognitive performance in patients with bipolar disorder and major depressive disorder are scarce.

Aripiprazole is an atypical antipsychotic drug used to treat a variety of psychiatric disorders, including schizophrenia and other depressive disorders.[7,8] Due to its partial dopamine agonist properties, it has also been added to prescriptions to reduce prolactin concentrations in antipsychotic-induced hyperprolactinemia. Thus, Aripiprazole is a potential treatment option for improving cognition and lowering prolactin levels in patients receiving prolactin-elevating antipsychotics.[9] However, only a few studies have been conducted on switching to aripiprazole treatment to improve cognition in patients with schizophrenia.[10]

Similarly, risperidone is a novel antipsychotic that inhibits both dopaminergic and 5-hydroxytryptaminergic receptors.[11] In some reports, patients taking this drug have developed clinically significant hyperprolactinemia. In recent years, it has been increasingly used in the treatment of various psychiatric disorders.[12,13] It is classified as an atypical antipsychotic and belongs to a new chemical class, namely benzisoxazole derivatives. Although risperidone has fewer extrapyramidal side effects than older neuroleptic drugs, it appears to have a greater potential to cause hyperprolactinemia.[14] Several studies have found that this drug causes reversible, symptomatic hyperprolactinemia in both male and female patients. In some studies, risperidone has been identified as the primary cause of hyperprolactinemia induced by drugs.

According to studies, a pathophysiological feature of schizophrenia may be a dysregulation of the inflammatory immune response. Conversely, antipsychotic medications have been found to have an immunosuppressive effect in patients with schizophrenia; however, this has not been consistently observed in different studies.[15] Multiple factors that influence inflammatory immune

Cite this article: Dawood MN, Aldabbagh KA, Alsarraf Z. Inflammatory Thyroid Changes Following Serotonin Receptor Blocking in Experimental Rats. Pharmacogn J. 2023;15(1): 189-193.

activity, such as diet, smoking, and medications, may contribute to inconsistent results in clinical studies. Preclinical studies have found that atypical antipsychotics, such as risperidone, have significantly reduced tumor necrosis factor-α and interleukin-6 production in microglia following interferon exposure, as well as in mice following peripheral lipopolysaccharide administration.[16,17] These preliminary findings suggest that atypical antipsychotics suppress inflammatory immune activation in response to exogenous stimuli.

The purpose of the following study is to compare the effects of risperidone with Aripiprazole on thyroid function as it relates to inflammatory markers (CRP).

MATERIALS AND METHODS

Chemicals: aripiprazole is used to treat psychiatric disorders such as schizophrenia, major depressive disorder, and bipolar I disorder, either alone or in combination with other medications. The chemical formula of aripiprazole is $C_{23}H_{27}C_{l2}N_3O_2$ with a molecular weight of 448.4 g/mol.

Risperidone is known as an atypical antipsychotic drug used to treat schizophrenia that works in the brain. It is also known as a second-generation antipsychotic (SGA). Risperidone restores the balance of 5-hydroxytryptamine and dopamine to improve cognition, behaviour, and depressive disorders. The chemical formula of Risperidone is found to be $C_{23}H_{27}FN_4O_2$ known molecular weight 410.5 g/mol.

Animal: Thirty healthy and disease-free male Sprague Dawley albino rats were used as the sample animal for this research. Each rate reportedly weighed between 200g to 300g.

Study design: This study was based on a randomized controlled trial. A total of thirty rats were recruited for the experiment and were kept in the artificial, and optimal environment. The temperature of the environment was maintained in the range of 5°F to 75°F which is approximately 18°C to 28°C. The observed humidity of the area was 30% to almost 70%. The rats were provided with food in a defined time and there was free access to water.

The rats were divided into three groups, each group had an equal number of rats which was 10 rats each. The first group was the control group which received the placebo, in the second group, there were 10 rats too, which was known as the risperidone group. Each rat received 20mg/kg/day through I/V. The third group is known as the aripiprazole group which received the drug from an intravenous route, 10mg/kg//day.

Biochemical investigation: To evaluate the impact of both drugs including Risperidone and aripiprazole on the thyroid hormones, ELISA for measuring thyroid hormones (kit supplied by AIA-PACK Assays - Tosoh Bioscience) were used. The levels of T3, T4 and TSH were recorded individually for each group.

Statistical analysis: The mean value for all the findings was recorded with the standard deviation. Furthermore, to evaluate the statistical difference between the theoretical values and obtained experimental values, a two-sided t-test has been used. To establish the difference and the comparison between the before and after, Paired t-test was used.

RESULTS

The results of the thyroid function test of each group, before and after the treatment are evaluated and represented in Figure 1. T3, or triiodothyronine, is a thyroid hormone. It has an effect on almost every physiological process in the body, including heart rate, individual growth and development, metabolism, and homeostasis, including body temperature.

In the controlled group, the value of T3 was found to be 0.4 ng/ml before, and the value remained the same after 6 weeks as well. In the case of the Aripiprazole group, the recorded value of T3 was 0.5 initially, and after the treatment, it was seen to fall to 0.3. Lastly, In the Risperidone group, the initially observed value of T3 was 0.3 which remained maintained after the treatment as well.

However, on the evaluation of free T3 pg/ml, in the controlled group, the values were observed to increase from 1.6 pg/ml to 2 pg/ml, respectively. In the case of the Aripiprazole group, the values increased from 2 to 2.1 respectively. Meanwhile, in the risperidone group, the

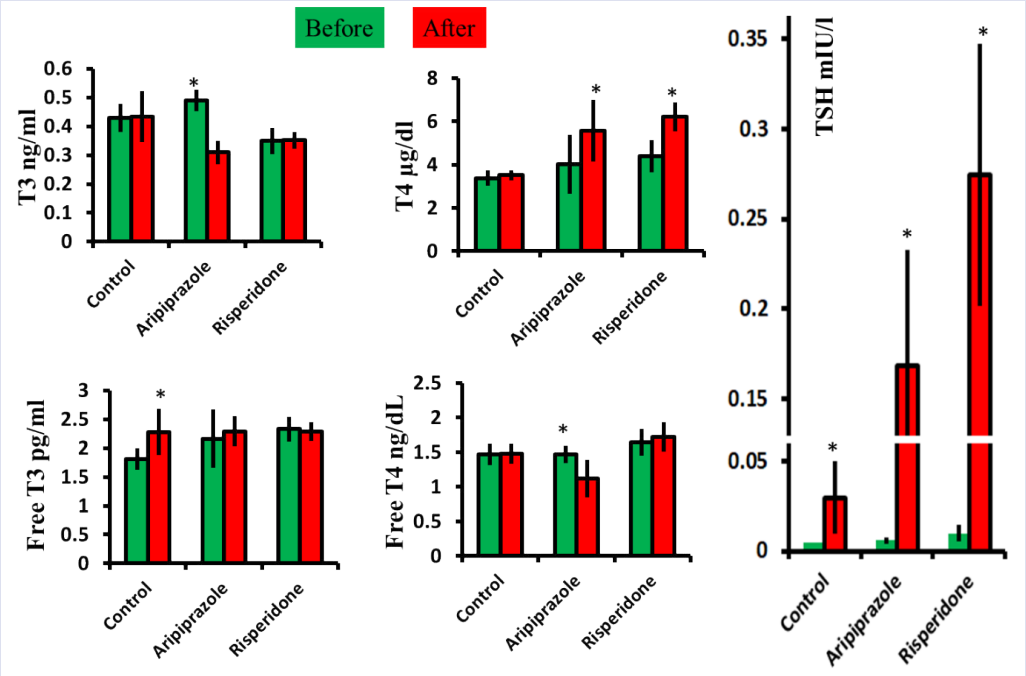


Figure 1: Thyroid function tests in experimental rat models after treatment with Aripiprazole, Risperidone compared to control group. Data expressed as mean±SD, *p<0.05. * as compared to before therapy or control groupT3=Triiodothyronine, T4=levothyroxine, TSH=thyroid stimulating hormone.

Table 1: CRP in experimental rat models after treatment with Aripiprazole, Risperidone compared to control group.

	Before	After
CRP	mean	mean
Control	< 3.0	< 3.0
Aripiprazole	< 3.0	< 3.0
Risperidone	< 3.0	< 3.0

values before and after the treatment remained almost constant at 2.4 pg/ml.

T4 also known as Thyroxine is a thyroid hormone too. It has similar functions as T3. The values of T4 and free T4 were also recorded in all three groups before and after the treatment. The recorded results represented that in the controlled group, the initial mean value of T4 was 3.38 and SD ± 0.35, while the values recorded after the treatment time were reported as the mean of 3.5 and SD ± 0.23. In the Aripiprazole group, the recorded mean value before treatment was 4 and SD ± 1.37, and 5.57 mean and SD ± 1.43 after the treatment of the drug. Lastly, in the Risperidone group, the mean value was 4.38 and SD ± 0.74, while after the treatment the mean was 6.2 and SD ± 0.66.

In the case of free T4 the values observed before and after the study duration in the controlled group were 1.46 and 1.48 respectively with SD ± 0.15 and ± 0.14. In the case of the Aripiprazole group, the mean value before the treatment was 1.47 with SD ± 0.13, and 1.12 SD ± 0.27 after the treatment. Lastly, in the Risperidone group, the values were 1.64, SD ± 0.19 and 1.722, SD ± 0.212 before and after the treatment respectively.

In the analysis of the values of TSH before and after the treatment in all three groups, the analyzed values in the controlled group were, mean = 0.005 and SD ± 0.00 before, and mean = 0.03 and SD ± 0.02 after the treatment. In The Aripiprazole group, the recorded values were mean = 0.001, SD ± 0.00 before, and 0.17 mean and SD ± 0.064 after. Lastly, In Risperidone group, the recorded values before the treatment were, mean = 0.009 and SD ± 0.00, mean = 0.27, and SD ± 0.07 after.

The summarized CRP values represented that all the mean values before and after the treatment remained less than 0.3 which is regarded as a normal cut-off value (Table 1).

DISCUSSION

Thyroid dysfunction is relatively common in patients with schizophrenia and other chronic depressive disorders, possibly due to the genetic relationship between these disorders and antipsychotic medications.[18] Many medications do interfere with biochemistry of thyroid function by interfering with the synthesis, transport and metabolism of thyroid hormones, or by altering the synthesis and secretion of thyroxine. Most patients with abnormal thyroid function tests are found to be clinically absent; however, these effects cause overt, clinically apparent thyroid disease in only rare cases.[19] The antipsychotics risperidone and aripiprazole are widely studied with respect to their impact on multiple aspects including the influence on hepatic function, renal function, the impact of the drug in the liver, and several other aspects.[2,20] Both of the following drugs have proven to be safe for clinical use under prescribed doses and conditions. In the following trial, the impact of aripiprazole and Risperidone has been studied in the levels of thyroid hormones including T3, T4, and TSH.

Higher than normal T3 levels usually indicate hyperthyroidism which is the over activity of the thyroid. Thyroid nodules, Graves' disease characterized as an autoimmune disease, and thyroiditis is all possible causes of hyperthyroidism, which is characterized by an inflammation of the thyroid gland. The results of the study indicated that there was no significant increase in the level of T3 before and after the treatment of rats for 6 weeks. These findings have been supported by multiple other studies which indicate that the use of aripiprazole does not cause fluctuations in the level of T3. However, these results were contraindicated by some other studies which indicated that aripiprazole increases thyroid-stimulating hormone levels and is associated with hyperprolactinemia.[21] Convulsions are a common neuropsychiatric disorder in children characterized by sudden, rapid, repetitive, rhythmless, and stereotypical motor activity and/or vocalizations. In contrast to this, based on blood analysis, the concentration of prolactin-releasing hormone (PRL) and thyroid-stimulating hormone (TSH) in the target sample was extremely low.[22] Surprisingly, after discontinuation of aripiprazole, the subject regained partial remission and plasma TSH and PRL concentrations increased.

According to this pilot study, the addition of aripiprazole to the treatment of patients with severe psychosis may improve antipsychotic-induced hyperprolactinemia, at least in the short term. Antipsychotic-induced hyperprolactinemia is an adverse event that can put patients' health at risk in the long run.[23] There is evidence of the increased frequency of osteoporosis, breast cancer and possibly prostate cancer, and when accompanied by symptoms, it can lead to poor patient compliance or discontinuation of treatment.

The depression therapy using risperidone was reported to significantly increased serum thyroid stimulating hormone levels only after four to eight weeks of therapy.[24] However, in this study, it has been found that in 6 weeks there was no marked increase in the level of TSH.

According to most of the research and studies, and the findings of the following trial, it can be stated that there is an influence of long-term use of Antipsychotics including both aripiprazole and Risperidone. However, both drugs have a significant beneficial effect in treating mental disorders including depression.[25] Therefore, it can be said that although the subjects who receive the following results do not require regular or frequent monitoring of thyroid hormones in long-term use and the use of the drug in higher concentration there must be a check as long-term use is associated with hyperthyroidism. However, the surrounding milieu greatly impact the response to the therapy, therefore, when endogenously applied agents used their impact on thyroid is greatly under control of the cellular response due to proinflammatory/anti-inflammatory cytokine released[26,27] and greatly impact by localized tissue oxygenation.[28,29]

CONCLUSION

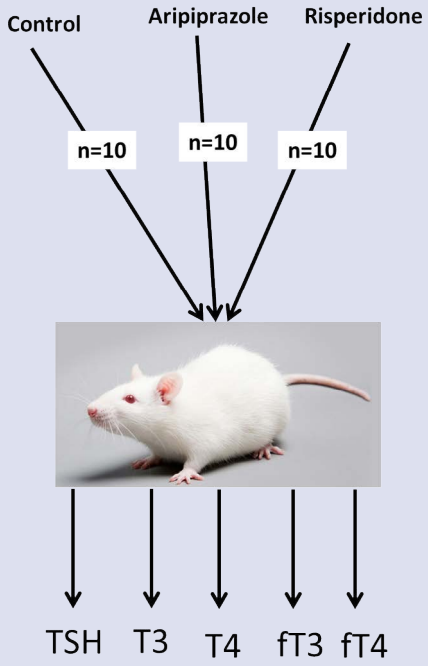
It can be concluded that both drugs are significantly effective in the treatment of psychiatric disorders, including depression. Therefore, it can be said that although subjects receiving the following results do not require regular or frequent monitoring of thyroid hormones, it is important to be checked in case of long-term use and use of higher concentrations of drugs, which are associated with hyperthyroidism.

REFERENCES

1. Brozman O, Kumari P, Runze L, Rysava T, Mikusova P, Novak J, *et al*. Towards the high-throughput assessment of thyroid hormone system disruptors. MMSL. 2022;91(Suppl.1):12.
2. Alvarez-Herrera S, Escamilla R, Medina-Contreras O, Saracco R, Flores Y, Hurtado-Alvarado G, *et al*. Immunoendocrine peripheral effects induced by atypical antipsychotics. Front Endocrinol. 2020;11(1):195.
3. Dai W, Liu J, Qiu Y, Teng Z, Li S, Huang J, *et al*. Shared postulations between bipolar disorder and polycystic ovary syndrome pathologies. Progress Neuro-Psychopharmacol Biol Psych. 2021;115:110498.
4. Naidoo V, Martínez-Iglesias O, Cacabelos R. Targeting epigenetics as future treatments of trauma-and stress-or-related disorders. Epidrugs and epinutraceuticals. InEpigenetics of Stress Stress Dis. 2022;317-92.

5. Bigio B, Zelli D, Lau T, de Angelis P, Miller D, Lai J, *et al*. ACNP 57th Annual Meeting: Poster Session I. 2018;43(1):77-227.
6. Naidoo V, Martínez-Iglesias O, Cacabelos R. Targeting epigenetics as future treatments of trauma-and stress-or-related disorders. Epidrugs and epinutraceuticals. InEpigenetics Stress Dis. 2022;317-92.
7. Voseckova A. Health psychology and mental hygiene. MMSL. 2003;72(6):273-5.
8. Vedal TS, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, *et al*. Free thyroxine and thyroid-stimulating hormone in severe mental disorders: A naturalistic study with focus on antipsychotic medication. J Psych Res. 2018;106(1):74-81.
9. Çöpür M, Çöpür S. Emergence of tic disorder in a pediatric patient associated with risperidone and aripiprazole treatment. Anadolu Psikiyatri Dergisi. 2019;20(6):671.
10. Can SS, Atagün Mİ, Çamur C, Uğurlu GK, İslamoğlu S. Extremely high prolactin level due to risperidone in a chronic renal failure patient. Klinik Psikofarmakoloji Bulteni. 2018;28:128.
11. Mullapudi M, Madan R, Vardhan V, Vidhyavathi M. Aripiprazole-induced Diplopia: A Rare Case Report. J Med Sci. 2019;5(3):73-4.
12. Güneş S, Ekinci Ö, Teke H, Yıldırım V. Risperidone related Raynaud's phenomenon: an adolescent case. Clin Psychopharmacol Neurosci. 2018;16(1):118.
13. Gundogmus I, Unsal C, Akgun A, Bolu A, Celik C, Uzun O. Risperidone-induced pretibial edema: A case report. 2020;27(1):429-30.
14. Tost M, Monreal JA, Armario A, Barbero JD, Cobo J, García-Rizo C, *et al*. Targeting hormones for improving cognition in major mood disorders and schizophrenia: thyroid hormones and prolactin. Clin Drug Inv. 2020;40(1):1-4.
15. Koller D, Almenara S, Mejía G, Saiz-Rodríguez M, Zubiaur P, Román M, *et al*. Metabolic effects of aripiprazole and olanzapine multiple-dose treatment in a randomised crossover clinical trial in healthy volunteers: association with pharmacogenetics. Adv Ther. 2021;38(2):1035-54.
16. Mejıa DK, Saiz-Rodrıguez M, Ochoa PZ, Navares-Gómez M, Pintos-Sánchez ES, Abad-Santos F. Metabolic Effects of Aripiprazole and Olanzapine Multiple-Dose Treatment in a Randomised Crossover Clinical Trial in Healthy Volunteers: Association with Pharmacogenetics. Adv Ther. 2021;38(2):1035-54.
17. Saarti M, Mahmood MD, Alchalaby LA. Comparative Effect of Aripiprazole Versus Risperidone on Sperm Motility and Morphology in Rats. Revista Electronica de Veterinaria. 2022;304-13.
18. Gundogmus I, Unsal C, Akgun A, Bolu A, Celik C, Uzun O. Risperidone-induced pretibial edema: A case report. 2020;27(1):429-30.
19. Hori H, Katsuki A, Atake K, Yoshimura R. Effects of continuing oral risperidone vs. switching from risperidone to risperidone long-acting injection on cognitive function in stable schizophrenia patients: a pilot study. Front Psych. 2018;9:74.
20. Thakur A, Niranjan V, Rastogi P, Razdan R. Acute oedema associated with risperidone use: a report. General Psychiatry. 2020;33(4):e100208.
21. Akan M. Development of enuresis secondary to risperidone: two case reports. Klinik Psikofarmakoloji Bulteni. 2019;29(1):241-2.
22. Śmierciak N, Szwajca M, Popiela TJ, Bryll A, Karcz P, Donicz P, *et al*. Redefining the Cut-Off Ranges for TSH Based on the Clinical Picture, Results of Neuroimaging and Laboratory Tests in Unsupervised Cluster Analysis as Individualized Diagnosis of Early Schizophrenia. J Personalized Med. 2022;12(2):247.
23. Patel RS, Heer AS, Lesko A, Kim SW, Ishaq M. Risperidone and Levothyroxine for Managing "Myxedema Madness". Cureus. 2020;12(8):e10152.
24. Vedal TS, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, *et al*. Free thyroxine and thyroid-stimulating hormone in severe mental disorders: A naturalistic study with focus on antipsychotic medication. J Psych Res. 2018;106(1):74-81.
25. Canfrán-Duque A, Pastor Ó, García-Seisdedos D, Molina YL, Babiy B, Lerma M, *et al*. The Antipsychotic Risperidone Alters Dihydroceramide and Ceramide Composition and Plasma Membrane Function in Leukocytes In Vitro and In Vivo. Int J Mol Sci. 2021;22(8):3919.
26. Shephard MT, Merkhan MM, Forsyth NR. Human Mesenchymal Stem Cell Secretome Driven T Cell Immunomodulation Is IL-10 Dependent. Int J Mol Sci. 2022;23(21):13596.
27. Chen L, Merkhan MM, Forsyth NR, Wu P. Chorionic and amniotic membrane-derived stem cells have distinct, and gestational diabetes mellitus independent, proliferative, differentiation, and immunomodulatory capacities. Stem Cell Res. 2019;40:101537.
28. Merkhan MM, Shephard MT, Forsyth NR. Physoxia alters human mesenchymal stem cell secretome. J Tissue Eng. 2021;12:20417314211056132.
29. Forsyth NR, Steeg R, Ahmad M, Al Zubaidi M, Al-Jumaily R, Merkhan M, *et al*. Mimicking Physiological Oxygen in Cell Cultures. InCell Culture Technol. 2018;129-37.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Muthear is currently a lecturer of Clinical Biochemistry at the department of Clinical Laboratory Sciences, College of Pharmacy at the University of Mosul, Mosul, Iraq. He has been graduated from college of Pharmacy, University of Mosul and He did his Master and PhD degree in Clinical Biochemistry in College of Medicine at the University of Mosul.

Karam is currently a lecturer of Microbiology at the department of Clinical Laboratory Sciences, College of Pharmacy at the University of Mosul, Mosul, Iraq. He has been graduated from College of Pharmacy, University of Mosul and He did his Master and PhD degree in Microbiology in College of Medicine at the University of Mosul.

Zahraa is currently a lecturer of Clinical Biochemistry at the Department of Pharmacy in Al-Hadba University College, Mosul, Iraq. She has graduated from College of Pharmacy, University of Mosul and she did her master degree in Clinical Biochemistry in College of Medicine at the University of Mosul.

Cite this article: Abid KY, Abachi FT. Phytochemical Comparative Studies, Antioxidant and Antimicrobial of Artemisia and Star Anise. Pharmacogn J. 2023;15(1): 189-193.