Research Article

Physiological Effect of Glycyrrhizic Acid on Adrenal Insufficiency Induces by Glucocorticoid in Rats

Wafaa AL. Bnyean[1,2] ,Zainab A.H. AL-Mousawi[1*]

[1]Department of Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, University of Basrah, Iraq; [2]Institute of Medical Technology of Baghdad, Middle Technical University, Iraq.

Abstract | This study investigates the efficacy of Glycyrrhizic acid (GA) against adrenal insufficiency caused by glucocorticoids in female rats. Fifty female rats were divided randomly into five groups. Negative control group(G1): Normal saline was given orally to rats. Positive control group(G2): rats for seven days were treated with Hydrocortisone Sodium I.P. (50 mg/kg). Therapeutic group(G3): rats for seven days were treated with Hydrocortisone Sodium I.P. (50 mg/kg) and then 14 days with GA (100 mg /kg) orally. Protective group(G4): Rats were treated for seven days with hydrocortisone Sodium I.P. (50 mg /kg) with GA for 14 days(100mg/kg) orally. glycyrrhizic acid Group (G 5): rats for 21 days, were given 100 mg/kg of GA orally. At the end of the experiment, Serum cortisol, ACTH, CRH hormone, 11 β -Hydroxysteroid Dehydrogenase enzyme (11β-HSD), and malondialdehyde were measured. The results revealed treatment with glycyrrhizic acid improved significantly (P<0.05) in serum cortisol, ACTH, CRH hormones, and (11β-HSD) enzyme concentration, while was a significant reduction in serum MDA level in the therapeutic and protective group compared with the positive control group. Our results concluded that glycyrrhizic acid improves the alteration caused by hydrocortisone of hypothalamus pituitary adrenal axis hormones and reduces the free radicals.

Keywords | Adrenal insufficiency, Glycyrrhizic acid, 11β-HSD, Hydrocortisone, Rats

Received | May 29, 2023; **Accepted** | June 20, 2023; **Published** | September 15, 2023
***Correspondence** | Zainab A.H. Al-Mousawi, Department of Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, University of Basrah, Iraq; **Email:** Zainab.hassan@uobasrah.edu.iq.
Citation | Al Bnyean W, Al-Mousawi ZAH (2023). Physiological effect of glycyrrhizic acid on adrenal insufficiency induces by glucocorticoid in rats. Adv. Anim. Vet. Sci. 11(10): 1667-1672.
DOI | http://dx.doi.org/10.17582/journal.aavs/2023/11.10.1667.1672
ISSN (Online) | 2307-8316

INTRODUCTION

Adrenal insufficiency (AI) is a clinical disorder that results in an inability of the adrenal cortex to produce or secrete cortisol. Adrenal insufficiency may primary (PAI) arise from secondary pathology of the adrenal gland which causes a defect at the adrenal level, secondary adrenal insufficiency (SAI) due to pathology of the hypothalamic or pituitary gland results in a defect at the pituitary level, or tertiary adrenal insufficiency (TAI) due to defect at the hypothalamic level as a result of inhibition of the hypothalamus pituitary adrenal axis via the therapy of exogenous glucocorticoids. PAI is also characterized by mineralocorticoid (aldosterone) deficiency (Kumar & Wassif, 2022; Martin-Grace et al., 2020). Synthetic glucocorticoids (GCs) due to their ability to reduce inflammation and inhibit the immune system, GCs are frequently employed, the potential glucocorticoid therapy side effect is inhibition of the hypothalamus pituitary adrenal axis resulting in adrenal insufficiency. Various factors are increasing the incidences of adrenal insufficiency caused by glucocorticoids such as the glucocorticoid dose, route of administration, the duration of glucocorticoid therapy, dosage and potency of glucocorticoid, synchronized medicines that interfere with glucocorticoid metabolism, and individual sensitivity. When the treatment of the exogenous glucocorticoid medication is lowered, pa-

tients may experience symptoms of Cushing's syndrome as well as glucocorticoid withdrawal syndrome. (Yasuda et al., 2019). So, before the return of adrenal function, the usage of glucocorticoids shouldn't be entirely ceased.

While prolonged utilization of exogenous glucocorticoids can cause atrophy of adrenocortical (zona fasciculata and zona reticularis atrophy) and pituitary corticotroph cells atrophy. Whereas mineralocorticoids are secreted to maintain aldosterone secretion, which is controlled by the renin-angiotensin system. (Prete & Bancos, 2021).

Glycyrrhizic acid (GA) is a triterpenoid complex that naturally extracts from the *Glycyrrhiza glabra* roots of licorice plants, which is thought to be a primary active and highly abundant component in licorice. Glycyrrhizic acid itself is hardly absorbed from the gastrointestinal tract. Before absorption, glycyrrhizin acid is hydrolyzed to give glycyrrhetic acid, which is the ultimate biologically active metabolite (Fernando et al., 2014). Researchers have reported the beneficial uses of GA at low precise doses; anti-diabetic, anti-hyperlipidemia, anti-inflammatory, antimicrobial, anti-viral, antioxidant and anti-tumor properties. Moreover, it also has hepato-protective, renal protective, neuro-protective effects, as well as tyrosinase and thrombin inhibitory activity, a steroid hormone, and estrogenic activity (Sun, et al. 2019). This research amid to detect the treatment and protective effect of Glycyrrhizic acid (GO) on hypothalamus pituitary adrenal axis hormones in adrenal insufficiency caused by glucocorticoids in female rats.

MATERIALS AND METHODS

Ethical Approval

This research was conducted in the animal house at the College of Veterinary Medicine, University of Basrah, Iraq. with the IACUC ethical approval for animal 7/37in 2022.

Chemical

Glycyrrhizinic acid 98% concentration was brought from China Animals: For this experiment, fifty female white rats (2-3 months) aged weighing 170-210 grams. The animal was housed in ventilated cages (10 rats /cages) under optimum conditions in the animal house including unlimited water and free use of a commercial diet. The animals were given 10 days to acclimatize to the lab environment.

Experimental design

Fifty female rats were divided randomly into five groups. Negative control group(G1): Normal saline was given orally to rats. Positive control group(G2): rats for seven days were treated with Hydrocortisone Sodium I.P. (50 mg/kg). Therapeutic group(G3): rats for seven days were treated with Hydrocortisone Sodium I.P. (50 mg/kg) and then 14 days with GA (100 mg /kg) orally. Protective group(G4): Rats were treated for seven days with hydrocortisone sodium I.P. (50 mg /kg) with GA for 14 days(100mg/kg) orally. Group 5 (glycyrrhizic acid): For 21 days, rats were given 100 mg/kg of GA orally. Blood samples from cardiac punctures were taken at the end of the trial and placed into gel tubes for hormonal and biochemical analyses.

Hormonal and biochemical assay

The serum cortisol, ACTH, and CRH hormone determination by using commercial kits (cobas / USA). Serum 11β-HSD enzymes (ELK Biotecohnolegy/China) and malondialdehyde (MDA) were determined by colorimetric method according to (Ahmed et al., 2011).

Statistical analysis

The data were statistically analyzed using the analysis of variance in the computerized SPSS program version 24.0.

RESULTS

Effect Of Glycyrrhizic Acid On Cortisol, Acth And Crh Hormones In Adrenal Insufficiency Female Rats.

The current investigation revealed a significant reduction($P<0.05$) in serum concentration of cortisol, ACTH, and CRH hormones in the G2 group injected hydrocortisone compared to the control (Table 1). Glycyrrhizic Acid treatment caused a significant increase ($P<0.05$) in G3(therapeutic)and G4 (protective) groups compared with the G2 group. However, the cortisol value in G3 and G4 groups and the ACTH value in the G3 group have significant differences ($P<0.05$) compared to the control. While no significant differences between G4 and the control group in ACTH and between G3, G4, G5 and the control group in CRH concentration (Figure. 1).

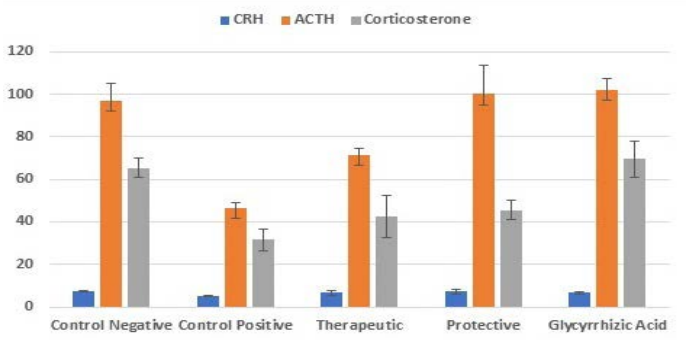

Figure 1: Effect of Glycyrrhizic acid on serum cortisol, ACTH, and CRH Concentration in adrenal insufficiency in rats. Control negative: received normal saline, control positive: hydrocortisone, Therapeutic: received hydrocortisone then Glycyrrhizic acid, Protective: received hydrocortisone with Glycyrrhizic acid, Glycyrrhizic Acid: Glycyrrhizic acid only.

Table 1: Effect of Glycyrrhizic acid on serum cortisol, ACTH, and CRH Concentration in adrenal insufficiency in rats .

Parameter/Group	Cortisol (nmol/L)	ACTH (Pg/ml)	CRH (Pg/ml)
Control Negative(G1)	65.22 ±4.58 a	96.88 ±8.34 a	7.42 ±0.30 a
Control Positive (G2)	31.51 ±5.03 c	46.57 ±2.64 c	5.13 ±0.5 b
Therapeutic (G3)	42.48 ±9.78 b	71.24 ±3.08 b	6.6 ±1.29 a
Protective(G4)	45.56 ±4.54 b	100.08 ±13.1a	7.21 ±0.99 a
Glycyrrhizic Acid(G5)	69.53 ±8.5 a	102.23 ±4.94 a	6.62 ±0.58 a

Values = mean ± SD., n = 10/group. Small letters = difference across groups P<0.05. Control group: received normal saline, Control Positive: hydrocortisone, Therapeutic: received hydrocortisone for 7 days then treated with Glycyrrhizic acid for 14 days, Protective: received hydrocortisone for 7days then Glycyrrhizic acid for14 days, Glycyrrhizic Acid: received Glycyrrhizic acid for 21days.

Effect Of Glycyrrhizic Acid On 11 B -Hydroxysteroid Dehydrogenase Enzyme In Adrenal Insufficiency Female Rats

The outcome revealed that the mean value of 11 β -Hydroxysteroid Dehydrogenase enzyme has decreased significantly (p<0.05) in G2 compared with the control and G5 groups. The effect of daily administration of glycyrrhizic acid indicates a significant rise (p<0.05) in the G3 and G4 groups compared with the G2 group and no statistical differences between the G3 group and the control (Table 2). Also, there was a significant increase in the G5 group treated with GA only compared to the control (Figure 2).

Table2: Effect of Glycyrrhizic Acid on 11 β -Hydroxysteroid Dehydrogenase Enzyme in Adrenal Insufficiency Female Rats

Parameter/Group	11 β-HSD (ng/ml)
Control Negative(G1)	0.423 ±0.06 c
Control Positive(G2)	0.141 ±0.04 d
Therapeutic (G3)	0.555 ±0.19 b c
Protective (G4)	0.706 ±0.14 b
Glycyrrhizic Acid(G5)	1.316 ±0.29 a

Values = mean ± SD., n = 10/group. Small letters = difference across groups P<0.05. Control group: received normal saline, Control Positive: hydrocortisone, Therapeutic: received hydrocortisone for 7 days then treated with Glycyrrhizic acid for 14 days, Protective: received hydrocortisone for 7days then Glycyrrhizic acid for14 days, Glycyrrhizic Acid: received Glycyrrhizic acid for 21days.

Effect Of Glycyrrhizic Acid On Mda Concentration In Adrenal Insufficiency Female Rats.

The results in Table (3) displayed that there was a significant increase(P≤0.05) in serum MDA concentrations in the adrenal insufficiency group (G2) compared to the control, G3, G4, and G5 groups. On the other hand, there were no significant differences G3 and G4 groups after being treated with glycyrrhizic acid compared to the control.

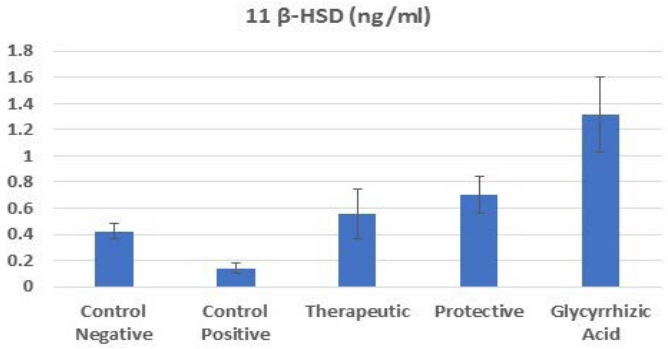

Figure 2: Effect of Glycyrrhizic Acid on 11 β -Hydroxysteroid Dehydrogenase Enzyme in Adrenal Insufficiency Female Rats. Control negative: received normal saline, control positive: hydrocortisone, Therapeutic: received hydrocortisone then Glycyrrhizic acid, Protective: received hydrocortisone with Glycyrrhizic acid, Glycyrrhizic Acid: Glycyrrhizic acid only.

Table (3): Effect of Glycyrrhizic Acid on MDA, concentration in Adrenal Insufficiency Female Rats.

Parameter/Group	MDA (nmol/L)
Control Negative	0.182 ±0 .04 b
Control Positive	3.58 ±0.718 a
Therapeutic	0.68 ± 0.17 b
Protective	0.39 ±0.09 b
Glycyrrhizic Acid	0.186 ±0.04 b

Values = mean ± SD., n = 10/group. Small letters = difference across groups P<0.05. Control group: received normal saline, Control Positive: hydrocortisone, Therapeutic: received hydrocortisone for 7 days then treated with Glycyrrhizic acid for 14 days, Protective: received hydrocortisone for 7days then Glycyrrhizic acid for14 days, Glycyrrhizic Acid: received Glycyrrhizic acid for 21days.

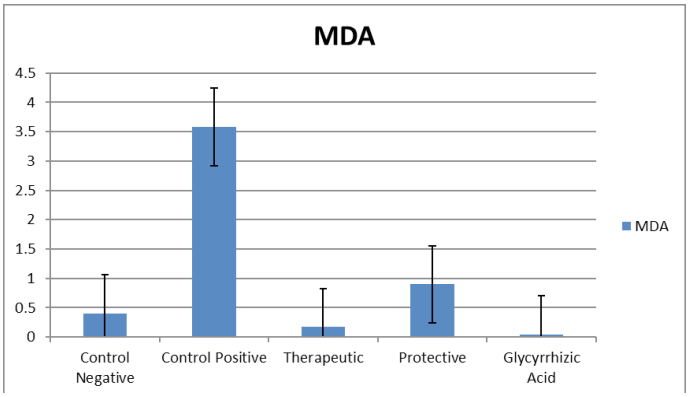

Figure 3: Effect of Glycyrrhizic Acid on MDA, concentration in Adrenal Insufficiency Female Rats. Control negative: received normal saline, control positive: hydrocortisone, Therapeutic: received hydrocortisone then Glycyrrhizic acid, Protective: received hydrocortisone with Glycyrrhizic acid, Glycyrrhizic Acid: Glycyrrhizic acid only.

DISCUSSION

Glucocorticoids induced adrenal insufficiency is one of the established models of drug-induced adrenal failure. Animal models are often used to understand the pathophysiology of AI and to test pharmacological therapy. In our study hydrocortisone injection for 7 days causes a significant decrease in the serum concentration of cortisol, ACTH and CRH. A similar finding from Leonie et al. (2015) demonstrated that exogenous hydrocortisone induces a negative impact on the hypothalamus and pituitary gland, resulting in a reduction of CRH and ACTH with the association of decreased cortisol production. Also, Téblick et al. (2022) found that in a sepsis mouse model, the plasma ACTH was suppressed after the administration of hydrocortisone. The pathophysiology of glucocorticoids is multifactorial, and it probably works through suppressed CRH, central noradrenergic and dopaminergic system, decrease in pro-opiomelanocortin related peptides due to chronic suppression of HPA axis, and increase in cytokines, and prostaglandins (Kao et al., 2010) and (Rensen et al., 2017). The administration of glycyrrhizic acid to groups treated with hydrocortisone a significant increase in corticosterone, ACTH and CRH levels and overcome the decreased levels that happened in the adrenal insufficiency group. Our findings support the earlier investigation (Lin et al., 2012) which demonstrated a higher concentration of cortisol levels in the male rats group treated with glycyrrhetinic acid than those of the adrenal insufficiency group. The authors supposed these criteria contributed to the inhibitory effect on 11β-hydroxysteroid dehydrogenase (11β-HSD).

From the results, the glycyrrhizic acid treated groups were an increase in the the11β-HSD concentration than the group injected with hydrocortisone only. The conversion of cortisol to cortisone and corticosterone to 11-dehydrocorticosterone by the enzyme 11-hydroxysteroid dehydrogenase (11-HSD) is crucial for controlling the transcriptional activity of the glucocorticoid and mineralocorticoid receptors. The ideal Inhibition of 11-HSD by glycyrrhetinic acid metabolites, bioactive components of licorice is endogenous steroidal substances acting as glycyrrhetinic acid-like factors that block 11-HSD dehydrogenase and enable glucocorticoid-induced MR and GR activation. Some GALFs, such as those that compete with cortisol and corticosterone dehydrogenation and the corresponding 11- and 7-oxo-derivatives that compete with cortisone and 11-dehydrocorticosterone oxoreduction, may act as competitive substrates, whereas others only function as inhibitors (Ramli et al., 2013, David et al., 2021). Moreover, glycyrrhetinic acid blocks the conversion of cortisol to inactive cortisone by suppressing 11β-hydroxysteroid dehydrogenase (Kim and Kim, 2016). Certain studies presented the selective inhibition of glycyrrhizic acid as it was found that 18α-GA preferentially selectively suppresses 11β-HSD-1, while 18β-GA preferentially inhibits 11β-HSD-2 (Ni et al., 2022).

Lipid peroxidation is caused by free radicals within an organism. One of the by-products of the peroxidation of polyunsaturated fatty acids in cells is Malondialdehyde. A rise in free radicals causes excessive production of MDA. So commonly malondialdehyde level is utilized as a biomarker for oxidative stress and the presence of antioxidants (Tyagi, et al., 2015, AL-Mousawi, 2021). From the results, of glucocorticoid injection, adrenal oxidative stress was proved by increased measuring MDA significantly. The glucocorticoids promote the production of free radicals such as relative oxygen species (ROS), which cause adrenal injury by oxidizing cell membrane lipids, denaturing proteins, and damaging DNA (Hasan and AL-Saeed, 2018). While. Treatment with GA attenuated the glucocorticoid-induced oxidative damage by reducing MDA levels. This could be explained by the ability of GA to modify certain enzymes involved in oxidative stress, inflammation, and the suppression of some pro-inflammatory cytokines, protecting cells from damage caused by ROS or inflammation. (Harikrishnan et al., 2021). The result agrees with (Gao et al., 2015, Xu et al., 2018; Yang et al., 2017) who reported that GA reduced serum levels of malondialdehyde (MDA) in rats. Additionally, many studies link the antioxidant property of GA with its anti-inflammatory action. In the model of lipopolysaccharide-stimulated microglial cells, it has been demonstrated that glycyrrhizin suppresses the generation of NO and inflammatory cytokines together with other elements of licorice extract (Fu et al., 2013; Yu et al., 2015).

CONCLUSIONS

From our result, we can conclude that Glycyrrhizic Acid has a beneficial effect in the treatment and protection of hormonal, biochemical and oxidation alterations in adrenal insufficiency rats induced by glucocorticoid.

ACKNOWLEDGMENTS

The authors sincerely thank the faculty and staff of the animal house at Basrah University College of Veterinary Medicine for their assistance and support.

CONFLICTS OF INTEREST

The writers state there is no conflict of interest.

NOVELTY STATEMENT

The study investigates the efficacy of Glycyrrhizic acid in therapeutic and protection against adrenal insufficiency caused by glucocorticoids in female rats. The results determined that glycyrrhizic acid improves and reduces the alteration caused by hydrocortisone of hypothalamus pituitary adrenal axis hormones and reduces the free radicals. According to the findings, glycyrrhizic acid may be efficient in adrenal gland function due to its effect on (11β-HSD) enzymes.

AUTHORS CONTRIBUTION

All authors contributed to the work that is being presented here. Each author has contributed to the idea and design of the study, data collecting, analysis and interpretation of the findings, and paper preparation.

REFERENCES

Ahmed J H., Al-Ahmed A. S., A Al-Masoodi E. (2011). Evaluation of the gastroprotective effect of misoprostol, chitosan and their combination on indomethacin induced gastric ulcer in rats. Med. J. Basrah Univ., 29(1): 1-8.

AL-Mousawi Z. A., AL-rikabi A. A., AL-Hamed H. A. (2021). Some Physiological Effect of Acacia Gum on Acute Renal Failure Induced by Gentamicin in Male Rabbits. Indian J. Forensic Med. Toxicol., 15(3): 3850-3855.

David J. Morris, Andrew S. Brem, Alex Odermatt (2021)., Modulation of 11β-hydroxysteroid dehydrogenase functions by the cloud of endogenous metabolites in a local microenvironment: The glycyrrhetinic acid-like factor (GALF) hypothesis. J. Steroid Biochem. Molecul. Biol. Volume 214105988, https://doi.org/10.1016/j.jsbmb.2021.105988

Fernando, H.A.; Chin, H.F.; Ton, S.H.; and Abdul Kadir, K.(2013). Stress and its effects on glucose metabolism and 11β-HSD activities in rats fed on a combination of high-fat and high-sucrose diet with glycyrrhizic acid. J. Diabet. Res. 2013,190395. https://doi.org/10.1155/2013/1903

Fu Y, Chen J, Li YJ, Zheng YF, Li P (2013). Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice. Food Chem. (2013);141(2):1063–71.

Gao Y.; Hao J.; Zhang H.; Qian G.; Jiang R.; Hu J.; Wang J.; Lei Z.; Zhao G. (2015). Protective effect of the combinations of glycyrrhizic, ferulic and cinnamic acid pretreatment on myocardial ischemia-reperfusion injury in rats. Experimen. Therapeut. Med., 9(2): 435-445. https://doi.org/10.3892/etm.2014.2134.

Harikrishnan, Basavegowda L (2021). Effects of Rhenium(I)-diselenoether and of its Diselenide Ligand on the Production of Cathepsins B and S by MDA-MB231 Breast Malignant Cells Antican. Res. December 41 (12): 5997-6001; https://doi.org/10.21873/anticanres.15418

Hasan Z. A., AL-Saeed M. H. (2018). Cardioprotective and Antilipidemic Role of *Ocimum basilicum s*eeds Oil and *Linum usitatissimum* Seeds Oil in Acute Myocardial Infarction Male Rabbits Induced by Isoproterenol. Basra J. Vet. Res., 17(3).

Kao TZ, Shyu MH, Yen GC. (2010) Glycyrrhizic acid and 18β-glycyrrhetinic acid inhibit inflammation via P13L/Akt/GSK3β signaling and glucocorticoid receptor activation. J. Agricult. Food Chem., 58, 8623-8629.

Kim J.H., Kim H. (2014). Combination treatment with herbal medicines and Western medicines in atopic dermatitis: Benefits and considerations. Chinese J. Integrat. Med., 22(5): 323-7. https://doi.org/10.1007/s11655-016-2099-0.

Kumar R., Wassif W. S. (2022). Adrenal insufficiency. J. Clin. Pathol., 75(7): 435–442. https://doi.org/10.1136/jclinpath-2021-2078951

Leonie H.A., Pereira B.A.M., Jørgensen J.O.L, Dekkers O.M. (2015). Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. J. Clin. Endocrinol. Metabol., 100 (6): 2171–2180. https://doi.org/10.1210/jc.2015-1218

Lin D.; Sun W.; Wang Z.; Chen L.G.; Chen X.L.; Wang S.H.; Li W.S.; Ge R.S.; Hu G.X. (2012). The effect of glycyrrhetinic acid on pharmacokinetics of cortisone and its metabolite cortisol in rats. J. Biomed. Biotechnol. 2012, 856324. https://doi.org/10.1152/ajpendo.00065.2001.

Martin-Grace J., Dineen R., Sherlock M., Thompson C. J. (2020). Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clin. Chim. Acta, 505: 78–91. https://doi.org/10.1016/j.cca.2020.01.029-

Ni Q.; Gao Y.; Yang X.; Zhang Q.; Guo B.; Han J.; Chen S. (2022). Analysis of the network pharmacology and the structure-activity relationship of glycyrrhizic acid and glycyrrhetinic acid. Front. Pharmacol., 13: 1001018. https://doi.org/10.3389/fphar.2022.1001018.

Prete A., Bancos I. (2021). Glucocorticoid induced adrenal insufficiency. BMJ., 374: 1–20. https://doi.org/10.1136/bmj.n1380

Ramli E.S.; Suhaimi F.; Asri S.F.; Ahmad F.; Soelaiman I.N. (2013). Glycyrrhizic acid (GCA) as 11β-hydroxysteroid dehydrogenase inhibitor exerts protective effect against glucocorticoid-induced osteoporosis. *J. Bone Miner. Metabol.*, *31*(3):262-73. https://doi.org/10.1007/s00774-012-0413-x.

Rensen N, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. (2017). Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia.

Cochrane Database Syst. Rev. 11:CD008727. https://doi.org/10.1002/14651858.CD008727.pub4

Sun Z. G.; Zhao T. T.; Lu N.; Yang Y. A.; Zhu H. L. (2019). Research progress of glycyrrhizic acid on antiviral activity. *Mini-Rev. Med. Chem.*, 19 (10): 826–832. https://doi.org/10.2174/1389557519666190119111125.

Téblick, A., Vander Perre S., Pauwels L. Derde S., Oudenhove T., Langouche L., Berghe G.(2021). The role of pro-opiomelanocortin in the ACTH–cortisol dissociation of sepsis. Crit. Care. (25) 65. https://doi.org/10.1186/s13054-021-03475-y

Tyagi A., Tyagi R., Choudhary P., Shekhawat J. (2015). Assessment of serum cortisol, malondialdehyde and free fatty acid levels in pre- and post-operative stress. International J. Clin. Experimen. Physiol., 2(1): 73.

Xu C.; Liang C.; Sun W.; Chen J.; Chen X. (2018). Glycyrrhizic acid ameliorates myocardial ischemic injury by the regulation of inflammation and oxidative state. *Drug Desig., Develop. Ther.*, 12, 1311-1319. https://doi.org/10.2147/DDDT.S165225.

Yang J.; Shi Y.; Chen H.; Wang X.; Chen Y.; Yang B. (2017). Glycyrrhizic acid attenuates myocardial injury: Involvement of RIP140/NF-kB Pathway. Biomed. Pharmacother., 95: 62-67. https://doi.org/10.1016/j.biopha.2017.08.031.

Yasuda A., Seki T., Kametani Y., Koizumi M., Kitajima N., Oki M., Seki M., Kakuta T., Fukagawa M. (2019). Glucocorticoid Receptor Antagonist Administration Prevents Adrenal Gland Atrophy in an ACTH-Independent Cushing's Syndrome Rat Model. Int. J. Endocrinol., 2019. https://doi.org/10.1155/2019/8708401

Yu JY, Ha JY, Kim KM, Jung YS, Jung JC, Oh S. (2015). Anti-Inflammatory Activities of Licorice Extract and Its Active Compounds, Glycyrrhizic Acid, Liquiritin and Liquiritigenin, in BV2 Cells and Mice Liver. Molecules. 20(7):13041–54.