Specialty Journal of Pharmacognosy, Phytochemistry, and Biotechnology
ISSN: 3062-441X
2023, Volume 3, Page No: 31-38

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Exploring the Wound Healing Potential of Aqueous Extracts from Caucasus Herbs in Diabetes Mellitus

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Received: 14 April 2023; **Revised:** 19 August 2023; **Accepted:** 24 August 2023

ABSTRACT

Diabetes mellitus is a common condition that often leads to serious systemic complications. This study investigates the healing of infected wounds in hyperglycemia using formulations derived from plant materials such as *Acacia nilotica*, *Trigonella foenumgraecum*, *Cyperus rotundus*, and *Cymbopogon proximus*. A model of dexamethasone-induced hyperglycemia was created, followed by wound induction and the application of *Streptococcus epidermidis*-infected material from a patient with streptoderma. The findings indicate that aqueous emulsions containing these plant extracts positively affected the dysmetabolic changes associated with dexamethasone-induced hyperglycemia, such as decreased hepatic transaminase activity and normalized blood glucose levels. In addition, the composition of peripheral blood improved with increases in erythrocytes and hemoglobin and a reduction in leukopenia. These changes provide a supportive environment for wound healing, overcoming the inhibitory effects of dexamethasone-induced injury on regenerative processes.

Keywords: Diabetes mellitus, Hyperglycemia, Caucasus herbs, Wound healing

How to Cite This Article: Tsiganock AS, Bgantseva AE, Vostrikova VR, Shevel DS, Saidarova AI, Bekbuzarov IM, et al. Exploring the Wound Healing Potential of Aqueous Extracts from Caucasus Herbs in Diabetes Mellitus. Spec J Pharmacogn Phytochem Biotechnol. 2023;3:31-8. https://doi.org/10.51847/Y5Fvcyw12s

Introduction

Diabetes mellitus is among the most prevalent conditions today, leading to significant systemic complications [1-3]. Elevated levels of corticosteroids trigger a series of catabolic processes that hinder the regeneration of epithelial tissues and the healing of wounds [4-6]. A balanced diet plays a key role in correcting the metabolic disturbances associated with diabetes [7, 8]. The most effective approach involves combining pharmacological treatments with nutritional strategies, which can include hypocholesterolemic, hypoglycemic, antioxidant, and immunomodulatory effects [9-11].

Phytotherapy, a well-established treatment in both conventional and traditional medicine, has garnered increasing attention because of its lower toxicity and broader acceptability, especially in regions with a rich history of herbal medicine [12-14]. Plants such as *Cymbopogon proximus*, *Trigonella foenumgraecum*, *Acacia nilotica*, and *Cyperus rotundus* exhibit a wide range of pharmacological benefits [15-18]. Notably, these include antiatherogenic, antidiabetic, anti-anorexic, antioxidant, anticancer, hypolipidemic, and anti-inflammatory properties [19-22].

In particular, for patients with type 2 diabetes or mild diabetes, phytotherapy is effective as a monotherapy, helping stabilize or even reverse the condition [23, 24]. Long-term use of herbal treatments improves patients' overall well-being and quality of life, reduces hyperglycemia, and may lead to a reduction in the need for antidiabetic medications, or even allow for their discontinuation [25, 26].

This study aimed to explore the regenerative processes of infected wounds in hyperglycemia using herbal formulations derived from Caucasus plants: *Acacia nilotica*, *Trigonella foenumgraecum*, *Cyperus rotundus*, and *Cymbopogon proximus*.

Materials and Methods

The experiment involved 35 nonlinear white rats, both male and female, weighing between 200-250 g. All procedures with the animals adhered to the *Guidelines for the Maintenance and Use of Laboratory Animals in the Russian Federation*.

Hyperglycemia was induced by administering 0.2 mL of a 4% dexamethasone solution intramuscularly for 4 days. The rats' back skin was treated with depilatory cream, cleaned, and then local anesthesia was applied using a 0.25% novocaine solution. Afterward, a 2 cm incision, 0.5 mm deep, was made with a razor blade [27]. Infected material from a patient diagnosed with streptoderma, containing *Streptococcus epidermidis*, was applied to the wound site twice.

The animals were randomly assigned to seven groups, each consisting of five rats. Group 1 was the intact control group. Group 2 was the first control group, with wounds treated with Vaseline. Group 3 was the second control group, where wounds were treated with fusidine. In group 4, the wound was treated with an emulsion containing *Cymbopogon proximus* while the rats were given an oral aqueous extract of *C. proximus*. Group 5 involved the application of an ointment made with *Cyperus rotundus* to the wound, alongside the oral administration of an aqueous extract of *C. rotundus*. Group 6 received an aqueous extract of *Acacia nilotica* orally, with an ointment based on *A. nilotica* applied to the wound. In group 7, rats were given an aqueous extract of *Trigonella foenumgraecum* orally, while an ointment made from *T. foenumgraecum* was applied to the wound.

On the fifth day of the experiment, the wound area was visually assessed for local changes based on semi-quantitative criteria such as compaction, roughness, pain upon palpation, hyperemia, swelling, and regeneration [28, 29]. The severity of each sign was scored on a scale, where the highest severity was assigned 5 points, and the absence of the sign received 0 points [30, 31].

Blood was drawn from the caudal vein and stabilized with a 10% sodium citrate solution. The blood composition and its biochemical parameters were analyzed using the PCE-90Vet analyzer (USA) for blood composition and the HUMASTAR 600 analyzer (Germany) for biochemical analysis [32, 33]. On the fifth day, the animals were euthanized in an ether chamber for anesthesia.

Statistical analysis was conducted using STATISTICA 12 software. A significance level of 0.05 was considered the threshold for testing statistical hypotheses. The statistical results are presented with the following indicators: M represents the sample mean, m (SEM) is the standard error of the mean, and p indicates the level of statistical significance.

Results and Discussion

It was observed that administering a dexamethasone solution at a dose of 800 µg/kg for 4 days resulted in the development of hyperglycemia in the rats **(Figure 1)**.

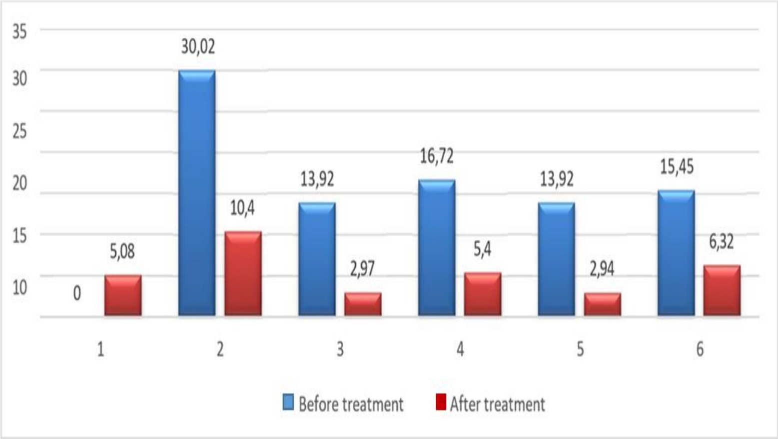

Figure 1. Dynamics of blood glucose levels in white rats with dexamethasone hyperglycemia and infected wounds during treatment with aqueous extracts (mmol/L): 1) intact, 2) dexamethasone solution, 3) dexamethasone solution + aqueous extract of *Cyperus rotundus*, 4) dexamethasone solution + aqueous extract of *Cymbopogon proximus*, 5) dexamethasone solution + aqueous extract of *Acacia nilotica*, 6) dexamethasone solution + aqueous extract of *Trigonella foenumgraecum*

An increase in glucose levels was observed in the rats, reaching 30.02 ± 5.16 mmol/L, compared to the initial 5.08 ± 1.18 mmol/L, with a P-value of < 0.001. When aqueous extracts were administered orally from the first day of dexamethasone treatment, glucose levels showed significant improvement. The most notable hypoglycemic effect was observed with the extracts of *Cyperus rotundus* and *Acacia nilotica* which reduced glucose levels by a factor of 2.74, with a P-value of < 0.001. In contrast, *Cymbopogon proximus* and *Trigonella foenumgraecum* extracts caused an increase in glucose levels by 304% and 329%, respectively, with P < 0.001.
After stopping dexamethasone treatment, the glucose levels in the untreated group decreased by 65%, reaching 10.4 ± 2.85 mmol/L, with a P-value of < 0.001. However, these levels remained nearly twice as high compared to the intact group, with P < 0.001, indicating ongoing hyperglycemia after dexamethasone administration. The oral intake of aqueous herbal extracts and the topical application of ointments resulted in a marked reduction in glucose levels, particularly with *Acacia nilotica* and *Cyperus rotundus*. Glucose levels were reduced to 6.32 ± 0.58 mmol/L and 5.4 ± 0.79 mmol/L, respectively, at P < 0.01. Interestingly, the use of fusidine was found to increase liver enzyme activity, with ALT rising by 341% and AST by 134%, both with P < 0.01, as seen in **Table 1**.

Table 1. Biochemical parameters of blood serum of white rats with hyperglycemia against the background of administration of dexamethasone solution with oral administration of aqueous extracts and local application of emulsions containing *Acacia nilotica*, *Cymbopogon proximus*, *Trigonella foenumgraecum*, and *Cyperus rotundus* (M ± m)

Index	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
ALT (units/L)	46.6 ± 9.22	41 ± 10.2*	209.5 ± 3.69*	128.5 ± 25.1#+*	207 ± 73.07+*	138 ± 32.1#+*	135 ± 37.7#+*
Albumins (g/L)	29.61 ± 0.8	29.7 ± 2.98*	31.5 ± 3.10*	34 ± 2.16+*	32.5 ± 4.04	32.25 ± 1.7	29.5 ± 3.69
AST (units/L)	137.1 ± 15.6	147.1 ± 20	302.5 ± 7.54*+*	271.25 ± 20#+*	124 ± 20.01#	208.7 ± 7.6#+*	245.2 ± 67.6+*
Creatinine (mg/dL)	0.04 ± 0.004	0.04 ± 0.005*	0.05 ± 0.005	0.04 ± 0.005	0.053 ± 0.003	0.045 ± 0.01	0.051 ± 0.009
Urea (mmol/L)	4.52 ± 0.51	5.2 ± 0.87	6.15 ± 0.33* #	8.6 ± 1.46#+*	12.37 ± 4.0#+*	10.1 ± 2.2#+*	11.35 ± 1.71#+*
Total protein (g/L)	55.33 ± 4.92	64 ± 5.61	60.5 ± 5.80	63 ± 6.78 +*	70 ± 7.3	64.7 ± 3.30	58 ± 5.22
Total cholesterol (mmol/L)	0.55 ± 0.08	1.3 ± 0.27*	1.47 ± 0.17 *	1.375 ± 0.27	2.25 ± 0.88+*	1.7 ± 0.29 +*	2.2 ± 0.38#+*
Triglycerides (mmol/L)	1.17 ± 0.83	1.09 ± 0.34	0.74 ± 0.23	1.02 ± 0.29	1.05 ± 0.32	1.37 ± 0.44#	0.79 ± 0.09

Note: * –statistical significance of the difference in the indicators of the group of intact animals at P < 0.05; # –statistical significance of the difference in the indicators of the group of animals treated with fusidine at P < 0.05; +* –statistical significance of the difference about the indicators of the control group at P < 0.05.

The extracts from *Trigonella foenumgraecum*, *Cymbopogon proximus*, and *Acacia nilotica* were found to reduce ALT activity by 34%, 35.5%, and 38.6%, respectively, with P < 0.001. In contrast, *Cyperus rotundus* extracts resulted in a 59% decrease in AST activity. Additionally, a significant rise in nitrogenous waste products was noted with fusidine (+18.2%), *Trigonella foenumgraecum* (+118%), and *Cyperus rotundus* (+137%), all with P < 0.001. Interestingly, the increase in urea was not accompanied by elevated creatinine levels, which suggests that the observed changes were not due to kidney dysfunction but were likely related to enhanced protein synthesis and improved liver function in urea production [34, 35].

Oral administration of *Acacia nilotica* aqueous extract led to a significant 14% increase in albumin levels (P < 0.001), while Trigonella foenumgraecum extracts resulted in a 49% increase in total cholesterol (P < 0.001). These beneficial metabolic shifts are likely contributing factors to the stimulation of repair and regeneration processes promoted by phytotherapy [36, 37].

In terms of peripheral blood analysis, fusidine treatment resulted in several abnormalities, including leuko-, lympho-, monocytopenia, and granulocytosis. The red blood cell count increased by 93%, hemoglobin levels rose by 148%, and platelet levels decreased by 38.8% when compared to the vaseline-treated group, with a significant P-value of < 0.001 **(Tables 2 and 3)**.

Table 2. Peripheral blood parameters of white rats with a wound process against the background of dexamethasone solution administration and fusidine treatment (M ± m)

Index	Groups		
	Intact	**Control (vaseline)**	**Fusidine**
Mean concentration hemoglobin (pg/L)	15.48 ± 1.33	15.85 ± 65	18.22 ± 1.77#
Mean corpuscular hemoglobin concentration (g/L)	263 ± 15.81	267.4 ± 16.59	293.2 ± 20.83 *#
Mean cell volume (fL)	60.38 ± 2.84	59.85 ± 3.02	62.3 ± 5.39
PLT, thrombocytes (× 10^9/L)	476 ± 12.20	474.6 ± 11.21	328.25 ± 38.23*#
Red cells distribution (%)	14.32 ± 0.85	14.1 ± 1.2	14.44 ± 0.21
Hematocrit (%)	16.72 ± 1.84	18.58 ± 3.65	41.6 ± 3.84 *#
Hemoglobin (g/L)	98.24 ± 11.83	50.6 ± 7.8*	125.8 ± 16.83 *
Granulocytes (%)	16.24 ± 6.8	24.43.7 ± 8.06	39.07 ± 6.66 *#
Granulocytes (units/L)	0.362 ± 0.10	0.36 ± 0.13	0.676 ± 0.1 *#
Leukocytes (× 10^9/L)	2.48 ± 0.33	2.42 ± 0.26	0.925 ± 0.15 *#
Lymphocytes (%)	75.84 ± 9.63	74.65 ± 11.19	31.25 ± 12.25 *#
Lymphocytes (units/L)	1.86 ± 0.29	1.85 ± 0.3	0.325 ± 0.1 *#
Monocytes (units/L)	0.124 ± 0.04	0.14 ± 0.05	0.05 ± 0.009 *#
Monocytes (%)	5.35 ± 1.84	6.22 ± 1.57	7.68 ± 2.2
Erythrocytes (× 10^{12}/L)	4.02 ± 2.15	3.06 ± 0.59	6.98 ± 0.41 *

Note: * –statistical significance of the difference about the indicators of the group of intact animals at P < 0.01; # –statistical significance about the indicators of the control group (vaseline) at P < 0.01.

The dosage forms containing *Cyperus rotundus* and *Cymbopogon proximus* effectively prevent the onset of leukopenia in control animals treated with fusidine, leading to a 95% and 215% increase in leukocyte count, respectively. However, the dosage forms containing *Trigonella foenumgraecum* and *Acacia nilotica* did not show any significant impact on the correction of leukopenia.

Table 3. Peripheral blood parameters of white rats with a wound process against the background of dexamethasone solution and fusidine treatment (M ± m)

Index	Control (fusidine)	*Cymbopogon proximus*	*Cyperus rotundus*	*Acacia nilotica*	*Trigonella foenumgraecum*	Control (vaseline)
Granulocytes (%)	39.07 ± 6.66*#	16.46 ± 5.82	29.83 ± 7.8+*	67.73 ± 10.0#+*	15.93.48#+*	24.43 ± 8.06
Granulocyte (units/L)	0.676 ± 0.1*#	0.23 ± 0.04 +*	0.6 ± 0.14 #	0.43 ± 0.17 +*	0.15 ± 0.05 #+*	0.36 ± 0.13
Leukocytes (× 10^9/L)	0.92 ± 0.15*#	2.9 ± 0.2 #+*	1.8 ± 0.56#+*	0.63 ± 0.2#	0.95 ± 0.1 #	2.42 ± 0.26

Lymphocytes (%)	31.25 ± 12.25*#	87.05 ± 2.8#+*	70.65 ± 3.14+*	11.51 ± 2.74#+*	76.77 ± 4.47 +*	74.65 ± 11.19
Lymphocytes (units/L)	0.325 ± 0.05*#	1.57 ± 0.47 +*	1.9 ± 0.53 +*	0.14 ± 0.06#	0.7 ± 0.08 #	1.85 ± 0.3
Monocytes (units/L)	0.05 ± 0.009*#	0.107 ± 0.075	0.125 ± 0.05+*	0.078 ± 0.025	0.097 ± 0.005+*	0.14 ± 0.05
Monocytes (%)	7.68 ± 2.2	1.7 ± 0.63#+*	3.8 ± 0.49#+*	10.55 ± 2.82 #	7.3 ± 1.46	6.22 ± 1.57
Thrombocytes (× 10^9/л)	328.25 ± 38.23*#	633.5 ± 160.8	2209.71 ± 316 #+*	1231.75 ± 377#+*	1040 ± 101.59#+*	474.6 ± 11.21

Note: * –statistical significance of the difference concerning the indicators of the group of intact animals at P < 0.01; # –statistical significance of the difference in relation to the indicators of the group of animals treated with fusidine at P < 0.01; +* –statistical significance of the difference in relation to the indicators of the control group (vaseline) at P < 0.01.

The emulsions containing *Cyperus rotundus* and *Cymbopogon proximus* led to a substantial increase in lymphocytes, by 484% and 383%, respectively. However, they did not have an impact on correcting granulocytopenia or monocytopenia. The application of *Acacia nilotica*, *Trigonella foenumgraecum*, and *Cyperus rotundus* significantly boosted platelet levels, increasing them by 3.76, 3.2, and 6.72 times, respectively, with P < 0.01. Additionally, the formulations with *Cymbopogon proximus*, *Trigonella foenumgraecum*, *Acacia nilotica*, and *Cyperus rotundus* helped sustain erythrocyte levels, which were comparable to the fusidine group (control) and significantly higher than those observed in the vaseline group (p<0.01), as detailed in **Table 4**.

Table 4. Peripheral blood parameters of white rats with a wound process against the background of the use of dexamethasone solution and treatment with dosage forms based on *Acacia nilotica*, *Cymbopogon proximus*, *Trigonella foenumgraecum*, and *Cyperus rotundus* (M ± m)

Index	**Control (fusidine)**	***Acacia nilotica***	***Cymbopogon proximus***	***Trigonella foenumgraecum***	***Cyperus rotundus***	**Control (vaseline)**
Mean concentration hemoglobin (pg/L)	18.22 ± 1.77+*	14.47 ± 1.82 #	18.37 ± 1.02+*	18.45 ± 2.25+*	18.77 ± 3.35	15.85 ± 65
Mean corpuscular hemoglobin concentration (g/L)	293.2 ± 20.11*+*	269 ± 44.50#+*	286.5 ± 16.2#+*	291.25 ± 22.4#+*	331.5 ± 58.0#+*	267.4 ± 16.5
Mean cell volume (fL)	62.3 ± 5.39	54.4 ± 2.59#+*	64.575 ± 7.22	63.825 ± 9.8	56.8 ± 0.75+*	59.85 ± 3.02
Red cells distribution (%)	14.44 ± 0.21	15.52 ± 0.94#+*	17.05 ± 2.88+*	14.72 ± 1.15	12.2 ± 0.80#+*	14.1 ± 1.2
Hematocrit (%)	41.6 ± 3.84*+*	22.2 ± 5.53 #	38.1 ± 5.64+*	40.55 ± 11.08+*	36.3 ± 14+*	18.58 ± 3.65
Hemoglobin (g/L)	125.8 ± 16.83+*	45.75 ± 7.22#	109.5 ± 20+*	116.75 ± 26.17+*	134.5 ± 14.70+*	50.6 ± 7.51*
Erythrocytes (× 10^{12}/L)	6.98 ± 0.41+*	5.39 ± 1.8+*	6.0 ± 1.40+*	6.44 ± 2.19+*	7.03 ± 1.67+*	3.06 ± 0.59

Note: * –statistical significance of the difference concerning the indicators of the group of intact animals at P < 0.01; # –statistical significance of the difference concerning the indicators of the group of animals treated with fusidine at P < 0.01; +* –statistical significance of the difference concerning the indicators of the control group (vaseline) at P < 0.01.

Herbal formulations containing *Cyperus rotundus*, *Cymbopogon proximus*, *Trigonella foenumgraecum*, and *Acacia nilotica* are effective in stimulating regeneration in wound healing. Their influence on wound repair in the context of dexamethasone-induced hyperglycemia is comparable to the effects observed with fusidine treatment [38, 39]. These plant-based treatments positively affected the various stages of the wound healing process, similar to the results from the use of fusidine ointment [40].

The antibacterial properties of *Acacia nilotica*, *Trigonella foenumgraecum*, *Cyperus rotundus*, and *Cymbopogon proximus* support the regeneration process. In addition, these herbs are noted for their immunomodulatory, hepatoprotective, antioxidant, and antitoxic effects, which are consistent with previous research findings [41-45]. For instance, *Cyperus rotundus* contains a variety of bioactive compounds, including alkaloids, flavonoids, essential oils, saponins, and other secondary metabolites [46, 47]. On the other hand, *Trigonella foenumgraecum* is a highly nutritious plant, and its regular consumption can contribute to strengthening the body’s immune response [48, 49].

Conclusion

The administration of aqueous emulsions containing *Acacia nilotica*, *Trigonella foenumgraecum*, *Cyperus rotundus*, and *Cymbopogon proximus* demonstrated a beneficial impact on the dysmetabolic disturbances associated with dexamethasone-induced hyperglycemia. These emulsions helped normalize blood glucose levels and reduced hepatic transaminase activity. Furthermore, they optimized the composition of peripheral blood by increasing erythrocyte and hemoglobin levels and alleviating leukopenia. These improvements provide a conducive environment for the repair processes, which are otherwise hindered by dexamethasone-induced damage. Consequently, the use of these Caucasus herbs can be considered a valuable adjunct in managing diabetes mellitus.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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