

ANTI-INFLAMMATORY AND HEPATOPROTECTIVE EFFECTS OF POLYHERBAL COMPOSITION IN PATIENTS WITH CHRONIC CHOLECYSTITIS

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*Herbal preparations are widely used in the complementary treatment of inflammatory diseases including hepatobiliary disorders, among which chronic cholecystitis is one of the most common. This study was aimed to investigate the effect of the water extract from polyherbal composition consisting of eight medicinal plants (*Helichrysum arenarium*, *Mentha piperita*, *Calendula officinalis*, *Taraxacum officinale*, *Polygonum aviculare*, *Matricaria chamomilla*, *Portulaca oleracea*, *Hypericum perforatum*) on biochemical and haematologic indices as well as on immune reactivity parameters in patients with chronic cholecystitis. It was found that consumption of polyherbal tea during 45 days was followed by normalization of liver biochemical indices (serum level of cholesterol, alanine aminotransferase and aspartate aminotransferase activity, total and unconjugated bilirubin levels and diminution of hematological (leukocytosis, increased erythrocyte sedimentation rate and neutrophil-to-lymphocyte ratio) and immunological (increased serum level of pro-inflammatory cytokines) signs of systemic inflammation in patients with hepatobiliary disorder. The results of the research showed that the studied polyherbal composition can be recommended as a component of the complementary therapy for patients with chronic cholecystitis.*

Key words: chronic cholecystitis, polyherbal composition, cholesterol, cytokines, hepatoprotective effect, immunomodulation.

Gallstone disease (cholelithiasis) remains one of the most cutting edge medical problems due to the steady increase in its frequency over the world. In the developed countries, cholelithiasis occurs in 10–20% of the population, and in 30–40% of elderly and old aged people [1]. Chronic cholecystitis (CC) is long-standing gallbladder inflammation that is associated with cholelithiasis in approximately 95% of cases. Pro-inflammatory activation of local (in gallbladder mucosa) and circulating immune cells with the overexpression of mediators such as endogenous alarmins (S-100) and

pro-inflammatory cytokines is considered as one of the putative pathogenetic mechanisms of the disease [2]. Neutrophils are recruited from circulation to the mucosa and affect interstitial Cajal-like cells, leading to impaired gallbladder motility. So, increased neutrophil-to-lymphocyte ratio (NLR) is a valuable prognostic factor of cholecystitis severity [3]. The first and top priority aim of treatment of chronic cholecystitis is the diminution of the inflammatory process, normalization of the bile secretion, concentration, and excretion, and prevention of gallstone formation. Herbal medicine remedies have an ability

to reduce gallbladder inflammation and are successfully used in the alternative treatment of gallbladder diseases [4]. Main objectives of the herbal treatment of chronic cholecystitis include improvement of bile discharge, elimination of spasms of the gallbladder and bile ducts, dissolution of the existing gallstones and prevention of their formation, as well as hepatoprotective and anti-inflammatory effects. One of the medicinal plants which has been widely investigated during the last two decades due to the unique properties is purslane (*Portulaca oleracea*). *Portulaca oleracea* is a cosmopolitan annual weed that has been listed in the World Health Organization as one of the most used medicinal plants. Pharmacological effects of *P. oleracea* are widely documented and include hypoglycemic, hypocholesterolemic, anti-diabetic, antipyretic, antiasthma, hepatoprotective, anti-inflammatory action etc. [5]. Phytochemicals of *P. oleraceae* include polyphenolics, flavonoids, alkaloids, tannins, saponins, vitamins A, E, C, fiber, coenzyme Q10, carotene, essential fatty acids, as well as calcium, zinc, potassium, sodium, manganese, iron, phosphorus and selenium [6]. This medicinal plants is more commonly used in the form of mono-component remedy. Though, herbal mixtures containing a combination of different medicinal plant have been reported to have better biological activities than isolated active compounds and monocomponent preparations due to the synergistic effect of their constituents [7]. Polyherbal composition, which combine pharmacological potential of eight medicinal plants (*Helichrysum arenarium*, *Mentha piperita*, *Calendula officinalis*, *Taraxacum officinale*, *Polygonum aviculare*, *Matricaria chamomilla*, *Portulaca oleracea*, and *Hypericum perforatum*) was developed in Nargiz Medical center (Republic of Azerbaijan) for the use as herbal tea and was patented in Eurasian Patent Organization, EAPO (EAPO Patent N 023163). This study was aimed to investigate the effect of polyherbal composition consisting of eight medicinal plants on biochemical and haematologic indices as well as on immune reactivity parameters in patients with CC.

Materials and Methods

Polyherbal composition. Studied polyherbal composition includes *Caléndula officinális* (flowers), *Polýgonum aviculáre* (flowers, leaves and stems), *Hypericum perforatum* (flowers and stems), *Taráxacum officinále* (roots), *Matricāria chamomílla* (flowers), *Helichrýsum arenárium* (flowers), *Méntha*

piperíta (leaves), *P. oleracea* (roots and leaf) which were taken in equal parts [8].

Patients and study design. Seventy six patients with CC without comorbidity associated with cytotoxicity (e.g. acute hepatitis A virus infection) who were appealed to Nargiz Medical Center of Baku, Azerbaijan for medical aid over a 2019 year were enrolled in the study (Table 1). Individuals were excluded if they had any of the following: received any medical treatment during the last month before the inclusion in the study; had been diagnosed with acute cholecystitis; were pregnant or breast-feeding. Those, who were not able to follow the instructions properly, were also excluded. The study was approved by the National Committee of Azerbaijan on the Bioethics of Scientific Knowledge and Technology at UNESCO (protocol N5, 12.11.2019). Written, informed consent was obtained from all patients according to a protocol of the National Committee of Azerbaijan on the Bioethics of Scientific Knowledge and Technology. All patients regardless of disease severity were included in the study.

The components of polyherbal composition were sealed in a teabag (5 g). Participants were provided with standard vessels (the volume of 200 ml) and were instructed to infuse the teabag in hot water in the vessel for 30 minutes, and then to drink the tea. They were instructed to drink the tea trice a day before the eating, for 45 days. Patient outcomes were recorded at baseline, and at the 30 days post-intervention follow-up. The outcomes of this study were haematologic indices, laboratory tests on liver, cytokine profile of peripheral blood, plasma myeloperoxidase, its activity and specific activity. Data on any unfavorable events were assembled at each visit.

Twenty healthy adults were recruited to participate in the study as a control group. Exclusion criteria was a history of somatic disease. Approval was obtained from the Ethical Committee of the Na-

Table 1. Baseline characteristics of the studied group

Female, %	63.1
Female age range, years	22-70
Male, %	36.9
Male age range, years	20-62
Calculous cholecystitis, %	61
Acalculous cholecystitis, %	39

tional Committee of Azerbaijan on the Bioethics of Scientific Knowledge and Technology at UNESCO, and consent was obtained from all healthy persons prior to the enrolment.

Haematologic assay. Haematologic indices included total count of leukocytes, segmented neutrophil (%), lymphocytes (%), eosinophils (%), monocytes (%) and NLR ratio, and were examined with the use of haematologic analyzer RT-7600 (Rayto Electronics, China) in accordance with manufacturer recommendations. In addition, all mentioned above haematologic indices along with band (immature) neutrophil (%) were determined in peripheral blood smears by routine manual method.

Biochemical assay. Biochemical indices included levels of serum cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBR), conjugated [direct reacting] and unconjugated [indirect reacting] bilirubin, and were examined with the use of Biochemical analyser KENZA Max BioChemistry (Biolabo SAS, France) in accordance with manufacturer recommendations.

Cytokine profile. Serum levels of interleukin-1 β , -6 and -4 (IL1 β , IL6 and IL4) were examined using ELISA kits (Vector Best, Russia) according to the manufacturer recommendations.

Myeloperoxidase detection. The total concentration of myeloperoxidase (MPO) and the concentration of active enzyme in the EDTA-blood plasma were measured by sandwich variant immunoassay (ELISA) combined with SIEFED (Specific Immunological Extraction Followed by Enzymatic Detection) analysis [9]. MPO was bound via a specific monoclonal capturing antibody (Abcam, UK) to an ELISA plate, and its activity was measured using a substrate mixture (20 μ mol of hydrogen peroxide, 50 μ mol of Amplex Red (10-acetyl-3,7-dihydroxyphenoxazine) in 50 mM phosphate buffer, pH 7.4 containing 50 mM NaBr) which gives a fluorescent product resorufin, measured using. The excitation wavelength is 544 nm and the wavelength of the emitted light is 590 nm. The concentration of active MPO (ng/ml) was determined according to a calibration curve constructed using standard solutions of human MPO (PLANTA ζ Austria). The plate was then washed and rabbit monoclonal antibodies against human MPO - detecting antibody (Abcam, United Kingdom) - was added. Immune complexes were visualized using biotinylated goat antibodies against rabbit immunoglobulin Fc fragment and

avidin-alkaline phosphatase conjugate (Dako, Denmark). The total concentration of MPO was determined using a calibration curve constructed using standard solutions of the enzyme. The results are expressed as three indices: the total level of MPO (ng/ml), the level of active MPO (ng/ml) and the relative amount of active MPO (%), calculated by the formula:

$$\text{active MPO (\%)} = (\text{active MPO concentration} \times 100) / \text{total MPO concentration.}$$

Statistical analysis. All data are presented as the mean and standard deviation. Baseline characteristics between two groups, as well as data before and after the intervention were compared using Student *t*-test and the Mann–Whitney U test for normally and non-normally distributed data, respectively. A *P* value ≤ 0.05 was considered statistically significant.

Results and Discussion

Medicinal plants included in polyherbal composition (PC) are characterized by potent immunomodulatory and anti-inflammatory activities [10]. Qualitative and quantitative phytochemical analysis of PC revealed tannins, saponins, flavonoids, water soluble and water insoluble phenolic compounds, cardiac glycosides and coumarins. Most predominant fatty acids were octadecadienoic (11.46 mg/g), octadecatrienoic (10.61 mg/g) and hexadecanoic (7.04 mg/g). No cytotoxic effect of PC was detected in our previous experiments *in vitro* [11]. Our results showed that the cholesterol, ALT and AST baseline serum levels significantly exceed the reference values in all patients with chronic cholecystitis, especially in woman (Table 2). Deviations from the norm in the levels of these indexes especially cholesterol were more pronounced in patients with calculous cholecystitis (data not shown).

Numerous clinical observations revealed positive association between the increased serum level of cholesterol and cholelithiasis [12]. Increased ALT and AST levels are also indicators of cholestasis [13], which along with elevated cholesterol serum level promote cholelithiasis and gallbladder inflammation. Additional risk factor of cholelithiasis is elevated serum level of unconjugated bilirubin in all study participants, since presence of unconjugated bilirubin plays an important part in the formation of cholesterol gallstones [14]. Treatment with polyherbal tea resulted in the normalization of mentioned biochemical constants in all patients with chronic

Table 2. Effect of water extract from polyherbal composition on serum biochemical indices of patients with chronic cholecystitis

Biochemical index	Reference values	Baseline value	Post-intervention value
<i>Female, n = 48 (age range 22-70 years)</i>			
Cholesterol, mg/dl	< 200	247.3 ± 37.1*	189.6 ± 9.4 [#]
ALT, IU/l	34	51.2 ± 12.6*	34.5 ± 2.6 [#]
AST, IU/l	31	44.1 ± 7.4*	30.1 ± 2.4 [#]
TBR, μmol/l	8-20	23.6 ± 4.2*	17.5 ± 1.1
Conjugated bilirubin, μmol/l	0-5	4.8 ± 0.7	3.9 ± 0.6
Unconjugated bilirubin, μmol/l	< 15	18.8 ± 3.8*	13.5 ± 0.6 [#]
<i>Male, n = 28 (age range 20-62 years)</i>			
Cholesterol, mg/dl	< 200	256.0 ± 35.3*	191.6 ± 7.1 [#]
ALT, IU/l	45	53.5 ± 8.0*	39.0 ± 3.3 [#]
AST, IU/l	41	41.9 ± 4.2	33.1 ± 1.5 [#]
TBR, μmol/l	8-20	23.2 ± 3.1*	17.4 ± 0.8 [#]
Conjugated bilirubin, μmol/l	0-5	4.8 ± 0.5	3.8 ± 0.5
Unconjugated bilirubin, μmol/l	< 15	18.0 ± 2.4*	13.0 ± 1.1 [#]

*The index is higher than reference values; [#]*P* < 0.05 as compared to the baseline value.

cholecystitis regardless of the form of the disease (calculous or acalculous).

Clinical data on hematologic indices in the course of chronic cholecystitis are sparse, since this form of the disease doesn't related to acute inflammation and dramatical changes in leukocyte count and proportions. In our experiments, total leukocyte count was slightly higher than upper value of reference range. It indicates low-grade or meta-inflammation that is typical for chronic diseases including hepatobiliary disorders [15].

Slightly elevated ESR was an additional indicator of low-grade inflammation in majority of study participants (Table 3). Fractions of leukocytes from different subpopulations didn't exceed control values. Though, baseline NLR ratio in our study participants with chronic cholecystitis was higher than that characteristic for healthy subjects [16].

NLR is one of the most popular biomarkers in biological and medical research in recent years. Association of NLR with numerous chronic inflammatory diseases is widely reported. NLR is both methodologically simple and affordable, and thus has been increasingly used in clinical trials and research studies. As mentioned above [3], NLR is considered informative marker of cholecystitis severity. In this study, NLR was significantly higher, when compared to the reference values, only in patients with

calculous cholecystitis (data not shown). Treatment with polyherbal tea resulted in the decrease of total leukocyte count to the middle value of the reference range. NLR after the tea consumption was lower than baseline value (1.8 times in male patients and 1.3 times - female) and didn't differ from reported in the literature normal values.

It should be noted, that significant individual variability in NLR and ESR was registered in the patients with acalculous cholecystitis. Comparative analysis of biochemical and hematological indexes of the patients did not revealed age-dependent differences both before and after consumption of polyherbal composition (data not shown).

Meta-inflammation is associated with moderate changes in local (in inflamed tissue) and systemic (in blood serum) cytokine profile [2]. In our experiments, three cytokines were examined: IL1β, IL6 and IL4. The examination was performed in three time points: before the intervention, 30 days after the start of tea consumption and at the end of the course of tea consumption. Our results have showed, that serum levels of all investigated cytokines were within reference rate but higher than median values stated by the manufacturer (Table 4). It is necessary to point that clinical investigation of blood donors by another research groups with the use of the same cytokine ELISA kits revealed higher values for healthy

Table 3. Effect of water extract from polyherbal composition on haematological indices of patients with chronic cholecystitis

Biochemical index	Reference values	Baseline value	Post-intervention value
<i>Female, n = 49 (age range 22-70 years)</i>			
Total leukocytes, 10 ⁹ /l	4-9	10.6 ± 2.9*	7.6 ± 0.9
Monocytes, %	3-11	4.2 ± 0.9	5.5 ± 1.3
Eosinophils, %	0-5	4.4 ± 1.2	3.3 ± 0.7
Segmented neutrophils, %	45-70	58.6 ± 3.2	55.9 ± 3.1
Band neutrophils, %	1-5	4.2 ± 1.0	3.5 ± 0.6
Lymphocytes, %	18-40	29.2 ± 2.3	30.6 ± 2.8
NLR	1.6 ^[16]	2.3 ± 0.4	1.8 ± 0.1
ESR, mm/hr	Women < 50 years old: < 20	21.2 ± 3.4*	10.6 ± 1.9 [#]
ESR, mm/hr	Women ≥ 50 years old: < 30	23.7 ± 4.8	10.9 ± 2.8 [#]
<i>Male, n = 28 (age range 20-62 years)</i>			
Total leukocytes, 10 ⁹ /l	4-9	10.6 ± 2.7*	7.2 ± 1.1
Monocytes, %	3-11	4.3 ± 0.8	5.7 ± 1.2*
Eosinophils, %	0-5	4.8 ± 1.3	3.6 ± 0.6
Segmented neutrophils, %	45-70	60.4 ± 3.8	54.7 ± 2.7
Band neutrophils, %	1-5	3.5 ± 1.1	3.5 ± 0.8
Lymphocytes, %	18-40	27.6 ± 3.1	31.5 ± 2.3
NLR	1.6 ^[16]	2.8 ± 0.3	1.6 ± 0.2 [#]
ESR, mm/h	Men < 50 years old: < 15	18.5 ± 2.9*	9.6 ± 2.1 [#]
ESR, mm/h	Men ≥ 50 years old: < 20	22.0 ± 1.0*	8.3 ± 0.7 [#]

*The index is higher than reference values; [#]*P* < 0.05 as compared to the baseline value.

Table 4. Effect of water extract from polyherbal composition on serum cytokine levels in patients with chronic cholecystitis

Cytokine	Control		Baseline	30 days	45 days
IL1 β	1.6 ± 0.2 (0-11)	Female, n = 20	6.2 ± 2.1*	4.4 ± 1.9*	5.2 ± 1.4*
	3.6 ± 1.0 ^[17]	Male, n = 11	8.0 ± 3.5*	5.6 ± 1.9*	5.0 ± 2.0*
IL6	2.1 ± 0.3 (0-10)	Female, n = 20	3.9 ± 1.5	2.0 ± 0.7	1.9 ± 0.5 [#]
	4.7 ± 0.9 ^[17]	Male, n = 11	5.3 ± 1.9*	2.7 ± 1.0	1.9 ± 0.5 [#]
IL4	0.2 ± 0.02 (0-4)	Female, n = 20	3.7 ± 1.6*	3.3 ± 1.7*	4.9 ± 2.3*
	0.6 ± 0.2 ^[17]	Male, n = 11	4.5 ± 2.0*	3.7 ± 2.0*	4.0 ± 1.9*

**P* < 0.05 as compared to the reference values; [#]*P* < 0.05 as compared to the baseline value.

persons as compared to those stated by the manufacturer [17].

Increased serum levels of IL1 β , IL6 indicate systemic inflammation. IL6 is considered as a 'metabolic hormone' and an attractive target for the treatment of metabolic diseases, since increased

level of this cytokine is regarded as a biomarker of systemic inflammation and metabolic disorders [18]. Consumption of polyherbal tea was associated with progressive decrease of IL6 serum level. Serum level of IL1 β didn't change in the study participants after the polyherbal tea consumption. One of the probably

Table 5. Effect of water extract from polyherbal composition on myeloperoxidase activity in patients with chronic cholecystitis

Parameter	Control		Baseline	30 days	45 days
MPO protein, ng/ml	10.6 ± 4.3	Female, n = 20	20.2 ± 7.1*	22.8 ± 7.9*	18.2 ± 6.4
		Male, n = 11	23.9 ± 8.5*	39.6 ± 9.4*	23.6 ± 10.0*
MPO activity, ng/ml	4.6 ± 1.8	Female, n = 20	2.4 ± 0.9	3.7 ± 1.0	2.3 ± 0.2*
		Male, n = 11	4.2 ± 1.9	8.5 ± 3.2*	2.3 ± 0.2*#
Specific activity of MPO, %	58.7 ± 20.3	Female, n = 20	16.7 ± 5.6*	20.3 ± 8.2*	13.5 ± 4.3*
		Male, n = 11	20.8 ± 7.3*	19.7 ± 8.0*	12.1 ± 4.9*

* $P < 0.05$ as compared to the healthy person's values; # $P < 0.05$ as compared to the baseline value.

reasons of this phenomenon can be the involvement of this cytokine in reparative processes in soft tissues [19].

Increased IL4 in blood serum can be the indicator of Th2 inflammation that is characteristic for the allergies, helminth infection etc. [20]. In addition, elevated IL4 level can evidence compensatory immune system response to chronic Th1 inflammatory process in order to induce alternative polarization of circulating and tissue mononuclear phagocytes, which are necessary for the tissue regeneration and inflammation resolution [21]. In our experiments, baseline serum level of IL4 was higher than normal values in all patients with chronic cholecystitis (Table 4). At the end of the course of polyherbal tea consumption, serum concentration of this cytokine was slightly increased. We incline to believe that slight increase in IL4 level along with the decrease in IL6 concentration can evidence anti-inflammatory effect of the intervention.

MPO is a well-known neutrophil enzyme, primarily released by activated cells and is characterized by potent pro-oxidative and proinflammatory properties. It is packaged in the azurophilic granules of neutrophils. The vital role of MPO is the host innate defense by the synthesis of oxidants such as hypochlorous acid. MPO is also released into the extracellular space during chronic inflammatory processes when neutrophils are activated and degranulate in the aseptic condition. In such cases, generated oxidants have significant potential to damage host tissue and are associated with many inflammatory diseases [22]. Currently, the level of circulating MPO is considered as an informative diagnostic and prognostic biomarker of pathological states associated with acute or chronic inflammation [23]. In our study, baseline total MPO level in blood

plasma of patients with chronic cholecystitis was significantly higher than that in healthy persons, especially in male patients (Table 5). At the same time, the percentage of active MPO was substantially decreased in all female patients. It can indicate metabolic exhaustion of innate immune cell associated with compensatory anti-inflammatory response syndrome (CARS), which is characteristic for the prolonged inflammatory processes, and can create a risk of opportunistic infections [24].

Polyherbal tea consumption was accompanied by transitory slight elevation of the levels of total and active form of MPO in blood plasma. However, indices of patients with chronic cholecystitis were still higher than those in healthy persons. At the end of tea course, all investigated parameters of plasma MPO did not differ significantly from corresponding baseline values.

In conclusion, our preliminary results suggest that a 45-day consumption of polyherbal tea consisting of eight medicinal plants including *P. oleracea* causes the normalization of liver biochemical indices, diminution of hematological and immunological signs of systemic inflammation, and in such a way can reduce the severity of chronic cholecystitis. Normalization of laboratory parameters was accompanied by the improvements in clinical outcome in 77.6% of participants (59 patients) as was confirmed by the results of ultrasonography and patient surveys. Clinical deterioration and/or adverse effects were not detected. These results give reasons to recommend investigated polyherbal tea as a component of complementary therapy for patients with this hepatobiliary disorder. Further studies with extended patient group are needed to elucidate comprehensively differences in the response to the polyherbal tea consumption in male and female patients.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ПРОТИЗАПАЛЬНИЙ ТА ГЕПАТОПРОТЕКТОРНИЙ ЕФЕКТИ ПОЛІГЕРБАЛЬНОЇ КОМПОЗИЦІЇ В ПАЦІЄНТІВ ІЗ ХРОНІЧНИМ ХОЛЕЦИСТИТОМ

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Препарати рослинного походження широко застосовуються у разі комплементарного лікування запальних захворювань, у т.ч. розладів гепатобіліарної системи, серед яких хронічний холецистит є одним із найпоширеніших. Метою роботи було дослідити вплив полігербальної композиції, яка містила 8 лікарських рослин (*Helichrysum arenarium*, *Mentha piperita*, *Calendula officinalis*, *Taraxacum officinale*, *Polygonum aviculare*, *Matricaria chamomilla*, *Portulaca oleracea*, *Hypericum perforatum*), на біохімічні та гематологічні показники, а також на параметри імунної реактивності в пацієнтів із хронічним холециститом. Встановлено, що споживання ними полікомпонентного чаю протягом 45 днів нормалізувало біохімічні показники печінки (рівень холестеролу, АЛТ, АСТ, загального та некон'югованого білірубину в сироватці крові) та зменшувало гематологічні (лейкоцитоз, підвищення ШОЕ та значення нейтрофільно-лімфоцитарного коефіцієнта), а також імунологічні (підвищений сироватковий рівень прозапальних цитокінів) показники системного запалення.

Зроблено припущення, що досліджена полігербальна композиція може бути рекомендована для застосування у комплементарній терапії хворих на хронічний холецистит.

Ключові слова: хронічний холецистит, полігербальна композиція, холестерол, цитокіни, гепатопротекторна дія, імуномодуляція.

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