UDC code: 616-002.1
DOI: https://doi.org/10.17816/MAJ60081

ANTI-CYTOKINE EFFECTS OF CHALCON ANALOGUES IN EXPERIMENTAL "CYTOKINE STORM" IN RATS

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For citation: Chernikov MV, Pozdnyakov DI, Rukovitsyna VM, Oganesyan ET. Anti-cytokine effects of chalcon analogues in experimental "cytokine storm" in rats. *Medical Academic Journal.* 2021;21(1):31–38. DOI: https://doi.org/10.17816/MAJ60081

Received: February 5, 2021 Revised: February 12, 2021 Accepted: March 15, 2021

The aim of the study was to evaluate the anti-cytokine effects of chalcon analogues in an experimental "cytokine storm".

Materials and methods. The "cytokine storm" was modeled in rats by intraperitoneal injection of lipopolysaccharide at a dose of 10 mg / kg. The test compounds and the reference drug dexamethasone were administered intraperitoneal 60 minutes after lipopolysaccharide injection at doses of 20 mg / kg and 3 mg / kg, respectively. After 24 hours, changes of the cytokines concentration in blood serum (IL-1β, IL-6, IL-10, and TNF-α), body temperature, and the severity of pulmonary edema were evaluated.

Results. In the study, it was found that the administration of all the test-compounds reduced symptoms of hypercytokinemia, reflected in the decrease in the concentration of proinflammatory cytokines IL-1β, IL-6, and TNF-α with high content of IL-10 in serum. At the same time, the body temperature and pulmonary edema in rats against the background of the injection of the test chalcon analogues relative to animals that did not receive pharmacological support also decreased. Against the background of the administration of dexamethasone to animals, the concentration of IL-6, IL-1β and TNF-α decreased by 25.0% ($p < 0.05$); 44.1% ($p < 0.05$) and 33.3% ($p < 0.05$), as well as an increase in the content of IL-10 by 60.0% ($p < 0.05$), with a decrease in pulmonary edema and body temperature. It should be noted that there were no statistically significant differences between the groups of animals that were received the studied chalcon analogues and the reference drug.

Conclusion. The study showed the relevance of further study of representatives of a number of chalcon derivatives as non-hormonal means of correcting the "cytokine storm" with a high therapeutic potential.

Keywords: inflammation; "cytokine storm"; chalcons, cytokines.

АНТИЦИТОКИНОВЫЕ ЭФФЕКТЫ АНАЛОГОВ ХАЛКОНА ПРИ ЭКСПЕРИМЕНТАЛЬНОМ «ЦИТОКИНОВОМ ШТОРМЕ» У КРЫС

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Для цитирования: Черников М.В., Поздняков Д.И., Руковицина В.М., Оганесян Э.Т. Антицитокиновые эффекты аналогов халкона при экспериментальном «цитокиновом шторме» у крыс // Медицинский академический журнал. 2021. Т. 21. № 1. С. 31–38. DOI: https://doi.org/10.17816/MAJ60081

Поступила: 05.02.2021 Одобрена: 12.02.2021 Принята: 15.03.2021

Цель исследования — оценить антицитокиновые эффекты аналогов халкона в условиях экспериментального «цитокинового шторма».

Материалы и методы. «Цитокиновый шторм» моделировали у крыс путем внутрибрюшинного введения липополисахарида в дозе 10 мг/кг. Исследуемые соединения и препарат сравнения — дексаметазон вводили интраперитонеально через 60 мин после инъекции липополисахарида в дозах 20 и 3 мг/кг соответственно. Через 24 ч оценивали изменение концентрации цитокинов в сыворотке крови (ИЛ-1β, ИЛ-6, ИЛ-10 и ФНО-α), температуры тела и выраженности отека легких.

Результаты. Было установлено, что введение всех исследуемых соединений уменьшало проявления гиперцитокинемии, выражающиеся в снижении концентрации провоспалительных цитокинов ИЛ-1β, ИЛ-6 и ФНО-α при увеличении содержания ИЛ-10 в сыворотке крови. В то же время температура тела и отек легких у крыс на фоне введения исследуемых аналогов халкона относительно животных, не получавших фармакологическую поддержку, также уменьшились. На фоне введения животным дексаметазона снизились концентрации ИЛ-6, ИЛ-1β и ФНО-α на 25,0 % ($p < 0,05$), 44,1 % ($p < 0,05$) и 33,3 % ($p < 0,05$), а также повысился уровень ИЛ-10 на 60,0 % ($p < 0,05$) при уменьшении отека легких и температуры тела. Следует

Abbreviations

IL – interleukin; IN – intact; LPS – lipopolysaccharide; NC – negative control; TNF-α – tumor necrosis factor-α.

отметить, что статистически значимых отличий между группами животных, которым вводили изучаемые аналоги халкона и препарат сравнения, выявлено не было.

Заключение. Исследование показало актуальность дальнейшего изучения представителей ряда производных халкона как негормональных средств коррекции «цитокинового шторма» с высоким терапевтическим потенциалом.

Ключевые слова: воспаление; «цитокиновый шторм»; халконы; цитокины.

Introduction

The infection caused by SARS-Cov-2, which has been spreading since the end of 2019, has shown that the vast majority of severe cases of the disease are associated with developing multiple organ failure mediated by the hypercytokine cascade collectively referred to as the "cytokine storm" [1]. The clinical manifestations of the cytokine storm vary depending on the disease onset and the therapy prescribed. In the acute phase, symptoms result from immune system hyperreactivity and tissue damage caused by cytokines and includes fever, anorexia, fatigue, arthralgia, myalgia, and dizziness. At the same time, further progression of immunopathological reactions leads to worsening of organ and tissue changes with the development of pulmonary edema, hypotension, hypoxemia, vascular collapse, hemostatic imbalance, and even death. In severe cases of the cytokine storm, which usually occurs without adequate treatment, renal failure, hepatobiliary dysfunction, and Takotsubo cardiomyopathy can develop. Neurotoxicity is observed several days after the cytokine storm onset and is associated with an increase in T-cell function [2].

Hyperreactivity of the immune system during the cytokine storm can be observed in the absence of a pathogen (genetic abnormalities), with excessive activation of peripheral immune cells (for example, with T-cell therapy), uncontrolled long-term activation of immunity (infection caused by the Epstein-Barr virus) or disorder of homeostatic immune mechanisms. Each of these conditions leads to uncontrolled production of proinflammatory cytokines with a decrease of anti-inflammatory mediators, such as interleukin (IL)-10 and cytokine decoy receptors presented by IL-1 receptor antagonists. As discussed, proinflammatory cytokines and the resulting cellular response play central roles in cytokine storm pathogenesis [3]. Several of these mediators have been identified by molecular cloning, including IL-1, IL-6, and tumor necrosis factor-α (TNF-α), high serum levels of which correlate with disease severity and mortality. IL-1, IL-6, and TNF-α provoke the development of fever, one of the leading early symptoms of the cytokine storm, through the activation of the intracellular signaling pathway Nf-κB-Akt. In addition to affecting Nf-κB and initiating an inflammatory response, TNF-α directly stimulates apoptosis and is one of the most potent triggers of hypercytokinemia. IL-6 is a cytokine with multitarget cell signaling, including JAK, STAT3, MAPK-ERK, and Akt-mTOR pathways. IL-6 leads to the hypersecretion of chemoattractant protein 1 (MCP-1), vascular endothelial growth factor, decreased expression of cadherins with the development of increased vascular permeability, edema, and pulmonary dysfunction [4].

Treatment strategies for the cytokine storm include the systemic administration of anticytokine agents represented primarily by glucocorticoids, IL-1 receptor antagonists (Anakinra), and IL-6 mediated cell signaling blockers (sarilumab, tocilizumab) that have an unfavorable toxicological safety profile [5]. At the same time, compounds containing chalcone scaffold are characterized by high anti-allergic and anti-inflammatory activity and anticytokine properties [6]. In this regard, five new analogs of chalcone were synthesized and were studied in this work as potential means to correct the cytokine storm in the experiment.

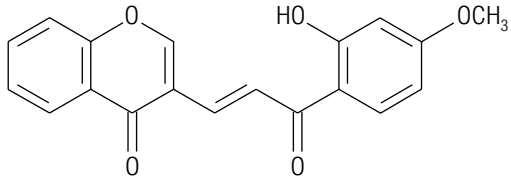
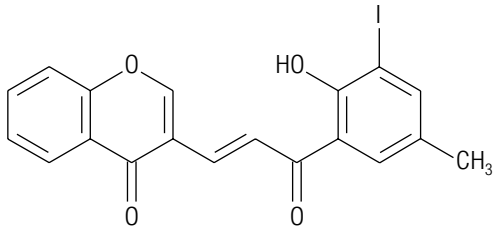
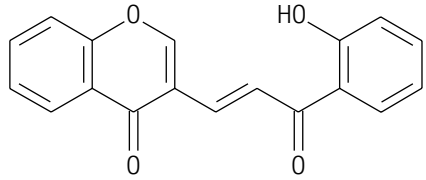
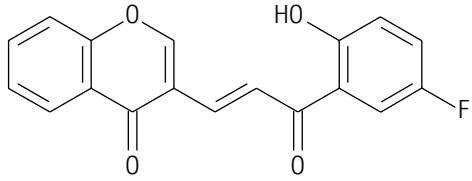
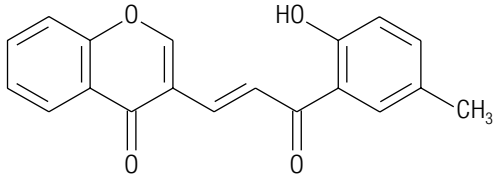
The aim of this work is to evaluate the anticytokine properties of five new chalcone analogs under the conditions of the cytokine storm in rats.

Materials and methods

The objects of the study in this work were five analogs of chalcone obtained at the Department of Organic Chemistry of the Pyatigorsk Medical and Pharmaceutical Institute under the guidance of Prof. E.T. Oganesyan, Dr. Pharm. Sciences. The structures of the study compounds were confirmed by nuclear magnetic resonance spectroscopy and are shown in Table 1.

Table 1 / Таблица 1

Structure of test-compounds
Структуры изучаемых соединений

	Structural formula	Laboratory code
1		X3A2OH4OCH3
2		X3A2OH3I5CH3
3		X3AphenOH
4		X3A2OH5F
5		X3A2OH5CH3

The cytokine storm was simulated in Wistar rats by intraperitoneal administration of lipopolysaccharide (LPS) (Sigma-Aldrich, Germany) at a dose of 10 mg/kg [7]. The animals were obtained from the Rappolovo nursery (Leningrad region) and were kept in quarantine conditions before being included in the study. The animal housing and procedures complied with the Directive 2010/63/EU of the European Parliament and the Study Animal Welfare Council. During the study, eight equal groups of rats were formed ($n = 10$ in each group): IN – intact animals; NC – negative control group (without pharmacological correction); rats that received a reference drug – dexamethasone (KRKA, Slovenia) at a dose of 3 mg/kg intraperitoneally [8]; animals administered study compounds as thin aqueous suspensions at a dose of 20 mg/kg intraperitoneally. The choice of study compound doses was based on previous trials [9]. The reference drug and the study agents were administered 60 minutes after the LPS injection. After 24 hours, the animals' body temperature was measured with a rectal thermometer. Then, blood was drawn from each rat's abdominal aorta and centrifuged at 1000 g for 20 min to obtain serum. The lungs were also removed from the animals. The change in the blood serum concentration of cytokines, IL-1β, IL-6, IL-10, and TNF-α, was assessed by the enzyme-linked immunosorbent assay. We used standard reagent kits for enzyme-linked immunosorbent assay manufactured by Cloud clone (USA). The severity of

pulmonary edema was determined by the loss on the drying method by calculating the hydration coefficient as recommended by Niu et al. (2019) [10]. The results obtained were expressed as the M (mean) ± SEM (standard error of the mean). The groups of mean values were compared using a one-way ANOVA with the Newman–Keuls post-test at $p < 0.05$. The statistical analysis was performed using STATISTICA 6.0 software (Statsoft, USA).

Results

During the study, the body temperature increased (Fig. 1) to 38.9°C 24 hours after LPS injection in rats of the NC group under an experimental cytokine storm ($p < 0.05$ versus IN rats). An increase in the serum concentration of proinflammatory cytokines IL-1β by 3.3 times ($p < 0.05$), IL-6 by 4.2 times ($p < 0.05$), and TNF-α by 3.9 times ($p < 0.05$) with a decrease in IL-10 by 72.3% was observed in NC group animals versus IN animals ($p < 0.05$) (Table 2). The hypercytokinemia in NC group rats was accompanied by significant pulmonary edema with an increase in the hydration coefficient (Fig. 2) by 40.5% ($p < 0.05$).

The use of dexamethasone decreased the body temperature to 37.8°C ($p < 0.05$ versus the NC group), the concentration of IL-6, IL-1β, and TNF-α decreased by 25.0% ($p < 0.05$), 44.1% ($p < 0.05$), and 33.3% ($p < 0.05$), and increased the IL-10 level (Table 2) by 60.0% ($p < 0.05$). The value of lung tissue hydration in rats (Fig. 2) that received dexamethasone was 22.0% lower than that in NC animals ($p < 0.05$).

Due to the administration of all studied compounds to rats, the severity of hypercytokinemia decreased. At the same time, the concentration of IL-6 decreased (versus the NC group) by 37.0% ($p < 0.05$), 31.5% ($p < 0.05$), 23.9% ($p < 0.05$), 22.8% ($p < 0.05$), and 42.4% ($p < 0.05$) when using compounds X3A2OH4OCH3, X3A2OH3I5CH3, X3AphenOH, X3A2OH5F, and X3A2OH5CH3, respectively (Table 2). There was also a decrease (versus the NC group) in the serum content of IL-1β by 31.6% ($p < 0.05$) due to administration of the compound X3A2OH4OCH3 to animals, by 48.5% ($p < 0.05$) – X3A2OH3I5CH3, by 43.4% ($p < 0.05$) – X3AphenOH, 30.9% ($p < 0.05$) – X3A2OH5F, and 52.9% ($p < 0.05$) – X3A2OH5CH3. The concentration of TNF-α in animals that received X3A2OH4OCH3, X3A2OH3I5CH3, X3AphenOH, X3A2OH5F, and X3A2OH5CH3 was lower than that in the group of rats without pharmacological support, by 50.7% ($p < 0.05$), 38.9% ($p < 0.05$),

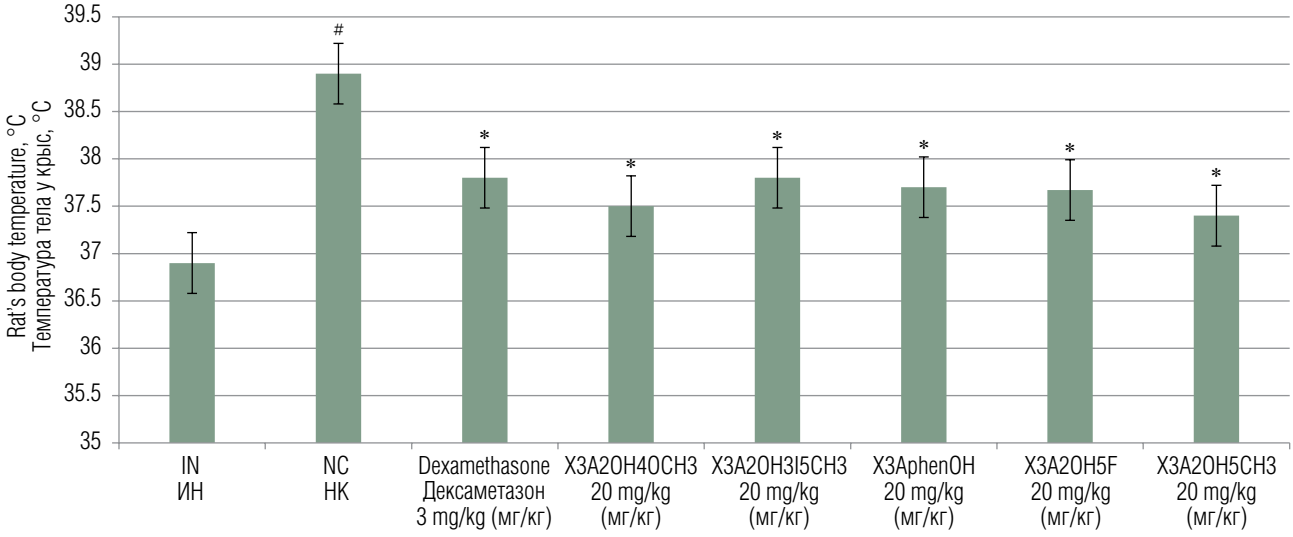


Fig. 1. Effect of the test-compounds and dexamethasone on changes in rat's body temperature under experimental "cytokine storm" conditions. IN — intact animals; NC — Negative control group; #statistically significant relative to intact animals (Newman-Keuls test, $p < 0.05$); *statistically significant relative to the negative control group (Newman – Keuls test, $p < 0.05$)

Рис. 1. Влияние исследуемых соединений и дексаметазона на изменение температуры тела у крыс в условиях экспериментального «цитокинового шторма». ИН — интактные животные; НК — группа негативного контроля. #статистически достоверно относительно интактных животных (критерий Ньюмена – Кейлса, $p < 0,05$); *статистически достоверно относительно группы негативного контроля (критерий Ньюмена – Кейлса, $p < 0,05$)

Table 2 / Таблица 2

The effect of the test-compounds and dexamethasone on the change in the concentration of cytokines in the blood serum in rats under the conditions of an experimental "cytokine storm"

Влияние исследуемых соединений и дексаметазона на изменение концентрации цитокинов в сыворотке крови у крыс в условиях экспериментального «цитокинового шторма»

Group	IL-6, pg/ml	IL-1β, pg/ml	IL-10, pg/ml	TNF-α, pg/ml
IN	2.2 ± 0.2	4.1 ± 0.7	9.4 ± 0.8	3.7 ± 0.1
NC	9.2 ± 0.3#	13.6 ± 0.5#	2.6 ± 0.8#	14.4 ± 0.2#
Dexamethasone, 3 mg/kg	6.9 ± 0.4*	7.6 ± 0.3*	4.2 ± 0.7*	9.6 ± 0.2*
X3A2OH4OCH3, 20 mg/kg	5.8 ± 0.4*	9.3 ± 0.5*	7.2 ± 0.6*	7.1 ± 0.6*
X3A2OH3I5CH3, 20 mg/kg	6.3 ± 0.3*	7.0 ± 0.3*	5 ± 0.8*	8.8 ± 0.5*
X3AphenOH, 20 mg/kg	7 ± 0.2*	7.7 ± 0.7*	5.4 ± 0.8*	9.4 ± 0.9*
X3A2OH5F, 20 mg/kg	7.1 ± 0.8*	9.4 ± 0.9*	4.3 ± 0.9*	8.7 ± 0.7*
X3A2OH5CH3, 20 mg/kg	5.3 ± 0.7*	6.4 ± 0.5*	6.8 ± 0.4*	7.3 ± 0.7*

Note. IN – intact animals; NC – negative control group. #statistically significant in relation to intact animals (Newman–Keuls test, $p < 0.05$); *statistically significant in relation to the negative control group (Newman–Keuls test, $p < 0.05$).

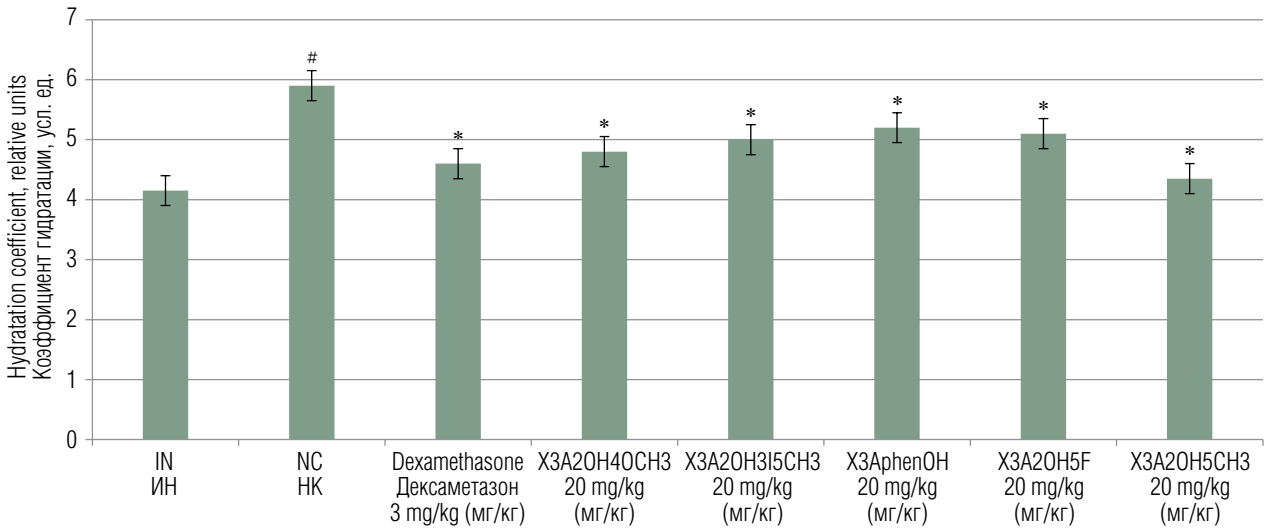


Fig. 2. The effect of the test-compounds and dexamethasone on the change in the severity of pulmonary edema in rats under the conditions of an experimental "cytokine storm". IN — intact animals; NC — Negative control group; #statistically significant relative to intact animals (Newman – Keuls test, $p < 0.05$); *statistically significant relative to the negative control group (Newman – Keuls test, $p < 0.05$)

Рис. 2. Влияние исследуемых соединений и дексаметазона на изменение выраженности отека легких у крыс в условиях экспериментального «цитокинового шторма». ИН — интактные животные; НК — группа негативного контроля. #статистически достоверно относительно группы интактных животных (критерий Ньюмена – Кейлса, $p < 0,05$); *статистически достоверно относительно группы негативного контроля (критерий Ньюмена – Кейлса, $p < 0,05$)

34.7% ($p < 0.05$), 39.6% ($p < 0.05$), and 49.3% ($p < 0.05$), respectively, with an increase of anti-inflammatory IL-10 level by 2.8, 1.9, 2.1, 1.7, and 2.6 times, respectively (all values $p < 0.05$ versus the NC group).

The body temperature in animals treated with studied compounds was significantly lower than that in the NC group (Fig. 1). In addition, the use of the studied analogs of chalcone contributed to a decrease in pulmonary edema versus the NC group by 18.9% ($p < 0.05$), 15.3% ($p < 0.05$), 11.9% ($p < 0. 05$), 13.6% ($p < 0.05$), and 27.1% ($p < 0.05$) due to administration of compounds X3A2OH4OCH3, X3A2OH3I5CH3, X3AphenOH, X3A2OH5F, and X3A2OH5CH3, respectively (Fig. 2).

Discussion

A cytokine storm is an uncontrolled immunopathological reaction with hypercytokinemia, multiple organ failure, and respiratory distress syndrome, which can be fatal. Today, the cytokine storm is the leading pathogenetic component of virus-mediated diseases, including respiratory infections, MERS, SARS, Dengue hemorrhagic fever, and Ebola fever. There is no doubt that it is necessary to perform targeted, rational pharmacotherapy [11]. In this case, as a rule, the treatment of the cytokine storm is limited to using glucocorticoids, which have an uncertain evidence level [12]. In this regard, five new analogs of chalcone were studied to assess the pharmacological effects of these compounds under the conditions of an experimental cytokine storm caused by intraperitoneal LPS administration. Intraperitoneally injected LPS causes the activation of the main proinflammatory signaling pathways, including Nf-κB-Akt and TLR-4-mediated signaling. This leads to a rapid increase in the cytokine blood level, development of oxidative stress, hypercoagulability, edema, and increased body temperature, reflecting the course of this pathological process in clinical practice [13]. As a result, it was found that the use of all studied compounds can reduce the hypercytokinemia phenomenon with a decrease in the serum concentration of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and an increase in the anti-inflammatory IL-10 level. Due to the administration of study compounds, a decrease in pulmonary edema and body temperature was noted compared with the animals without pharmacological support. No significant differences between the groups of rats that received the reference drug, dexamethasone, at a dose of 3 mg/kg and study compounds were established. This finding may indicate a high therapeutic potential of the studied analogs of chalcone. At the same time, despite the absence of significant differences, compounds containing a hydroxyl group in the second position and a methoxy group in the third position or a methyl group in the fifth position exhibited a slightly higher level of pharmacological activity than chalcones containing halogen atoms (I and F).

The anticytokine effects of compounds containing the chalcone scaffold may be related to the effect on IkB kinase activity. IkB kinase is a regulator of Nf-κB-dependent cell transduction which, in turn, is a critical component of the immune response [14]. A keto group conjugated with a π-bond in the chalcone derivative structure mediates a high affinity for the β-chain cysteine of the IkB kinase. It is inactivated in the Michael-type nucleophilic addition reaction, resulting in the enzyme losing its activity. At the same time, a decrease of IkB kinase catalytic properties prevents Nf-κB translocation into the nucleus, thereby suppressing the inflammatory response [15]. In addition, as pointed out by Zhang et al. (2017), chalcones can inhibit TLR-4-dependent transduction that prevents the proliferation and differentiation of immune cells, subsequently decreasing proinflammatory cytokine production [16].

Conclusion

This study showed that a single intraperitoneal administration of new chalcone analogs at a dose of 20 mg/kg contributed to the elimination of hypercytokinemia with a decrease of body temperature and pulmonary edema in animals with an LPS-induced cytokine storm. At the same time, the values obtained in association with using the studied compounds were comparable to the reference drug, dexamethasone, at a dose of 3 mg/kg. Thus, we can assume that the chalcone derivatives presented in this work as agents of non-hormonal structure for correcting the cytokine storm have relevance for further study.

Additional information

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

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