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Ўзбекистон Республикаси Вазирлар Маҳкамаси ҳузуридаги Олий аттестация комиссияси (ОАК) қарорига асосан «Stomatologiya» журнали Фан доктори илмий даражасига талабгорларнинг диссертация ишлари илмий натижалари юзасидан илмий мақолалар эълон қилиниши лозим бўлган республика илмий журналлари рўйхатига киритилган *(ОАК Раёсатининг 2013 йил 30 декабрдаги 201/3-сон қарори билан тасдиқланган)*

ТАҲРИРИЯТ МАНЗИЛГОҲИ:

100048, Ўзбекистон Республикаси,
Тошкент ш., Махтумқули кўчаси, 103
тел.: +99871-236-26-75;
факс: +99871-230-47-58
Интернетдаги манзилгоҳи:
stomjurnal.tibbiyot.com.

Дизайнер ва компьютерда терувчи:
Е.Алексеев
Муҳаррир О.А.Козлова
Баҳоси келишилган нархда.

Рекламани чоп қилиш ҳақ тўлаш йўли билан амалга оширилади.

Реклама матнининг тўғрилиги бўйича жавобгарлик реклама берувчи зиммасидадир.

Қўлёзмалар, суратлар ва расмлар тақриз қилинмайди ҳамда эгасига қайтарилмайди.

Келтирувчи фактларнинг тўғрилиги, рақамли материалларнинг аниқлиги, препаратларнинг номлари, атамалар, илмий-адабий манбалар, исм ва фамилияларнинг тўғрилиги учун жавобгарлик муаллифларнинг ҳамда таҳририят ҳайъатининг зиммасидадир.

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INTERLEUKIN LEVELS IN THE PATHOGENESIS OF CORONAVIRUS INFECTION (COVID-19) AND THE EFFECT OF A NEW COMBINATION DRUG (G. LUCIDUM AND ALKHADAYA) ON THE COURSE AND PROGNOSIS OF THE DISEASE


Abilov P.M., Makhkamova F.T.
Tashkent State Medical University

An out spike (S) glycoprotein on the virion surface that is essential for binding to the human angiotensin-converting enzyme 2 (ACE2) receptor and viral entry into the cell [7]. The envelope (E) protein likely forms viroporin , which is important for virus assembly and release, and is also a putative virulence determinant [5]. The membrane protein (M) is an abundantly expressed structural protein within the lipid envelope that is also important for viral morphogenesis and suppression of interferon synthesis [6]. Finally, the nucleocapsid protein (N) stabilizes the RNA genome in the helical complex and serves as a key target of adaptive immunity [8]. In addition, there are a number of accessory proteins, some of which have unknown functions. ORF3a may function as an apoptosis inducer [4]. ORF6 and ORF8 are involved in interferon antagonism, while ORF7a may be involved in inhibition of cellular translation [10]. ORF9b, an accessory protein, is translated from an alternative open reading frame in the gene. The steps of the SARS-CoV-2 replication cycle have been deduced from empirical data and existing knowledge of other β-coronaviruses [9]. The first step of SARSCoV-2 infection is the binding of the S protein to the soluble ACE2 receptor on the host cell surface. ACE2 is known to be expressed on the cell surface of various organs such as the heart, endothelium, liver, kidney, testicles, intestine, lungs and other tissues [6]. Other factors that facilitate viral attachment or entry include neuropilin-1, the UFO receptor tyrosine protein kinase (AXL), CD147, high-density lipoprotein receptor type B1, integrins, angiotensin II receptor type 1 (AT1) and vasopressin receptor subtype 2. Proteases such as surface TMPRSS2 and endosomal cathepsin L, cleave the S protein, activating viral entry into the cell by endocytosis and membrane fusion. Inside the cell, the virus loses its envelope and the genomic RNA enters the cytoplasm for further replication. Viral assembly occurs in the endoplasmic reticulum, Golgi complex, and intermediate complex (ERGIC), where membranes studded with viral structural proteins interact with the N-encapsulated viral genomic RNA.

Monocytes and macrophages also express ACE2 on their surface and can therefore be infected by SARS-CoV-2, which may lead to the activation and transcription of pro-inflammatory genes. ACE2 receptor expression has been detected on CD68+ and CD169+ macrophages in the lymph nodes and spleen of COVID-19 patients, suggesting that SARS-CoV-2 infects ACE2-positive myeloid cells throughout the body. CD169+ macrophages have been shown to be a site of viral replication, which significantly contributes to the level of viral replication as a result of the state of unresponsiveness to type I IFN-dependent activation , which may contribute

to reduced immunity, I proposed a combination of G. lucidum and Alkhadaya . The composition of this natural product is very wide, including superoxide dismutase, which also reduces the pathogenetic effect of the «cytokine storm» without causing side effects on the liver. I noticed that G. lucidum and Alkhadaya contain carboxyl groups in their composition, and they are not a continuation of nitro groups and sulfhydryl groups. These carboxyl groups depart from the phenolic rings of G. lucidum and the benzene rings of Alkhadaya, and the idea of creating a new drug based on G. lucidum was proposed, and Alkhadaya, and given such great importance not only in the treatment of coronavirus infection, but also in its safe use, then this study is considered a relevant topic and requires further study.

Purpose of the study

Determination of interleukin levels under the influence of a new combination drug based on G. lucidum and Alkhadaya.

Material and methods

To achieve the set goal, the results of treatment of 200 rats with coronavirus infection caused by COVID -19 were analyzed. Rats were intranasally infected with the SARS - Cov -2 strain 50% of the tissue culture median infectious dose (TCID 50) per 50 µl of inoculum (biological product with live cultures) after intraperitoneal anesthesia using a 2.5% sodium thiopental solution. All rats were divided into groups: Group 1 - rats with coronavirus infection with a confirmed positive PCR test, treated with ivermectin at a dosage of 300 mg of body weight (n = 50), Group 2 - rats with coronavirus infection treated with baicalin at a dosage of 500 mg (n=50), Group 3 - rats with coronavirus infection treated with molnupiravir 25 mg/kg of body weight, Group 4 - rats with coronavirus infection treated with a new drug based on G. lucidum and Alkhadaya. The quantitative profile of cytokines in blood serum was analyzed using Bio-Plex multiplex technology (io-Rad, Hercules, CA, USA). The concentration of 27 cytokines was measured: IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF basic, G-CSF, GM-CSF, IFN-g, IP-10, MCP-1(MCAF), MIP-1a, PDGF- bb, MIP-1b, RANTES, TNF-α, VEGF. Statistical processing was performed using one-way analysis of variance (one-way analysis of variance ANOVA) post Tukey's hoc test or two-way analysis of variance (two-way analysis of variance ANOVA) were used in the work for multiple comparisons between the tested groups. All analyses were performed in a blinded manner with respect to the experimental groups. A P value of <0.05 was considered statistically significant.

Results of the research

To determine the level of expression of cytokines and growth factors in coronavirus infection, taking into account different periods of the disease, a multiplex immunoassay was performed. This task was performed with the aim of subsequently identifying protein molecules that have the greatest impact on the modulation of the phenotype in coronavirus infection. The study revealed significant differences in the content of some analytes in coronavirus infection. The level of the proinflammatory cytokine IL-1β was significantly increased on day 3 in all studied groups with coronavirus infection compared to the intact control ($p<0.05$).

During the same period (day 14), the concentration of IL-4 in group 4 was also minimal, and differences were revealed when compared with group 3. On day 3 after infection, the maximum expression of TNF-α was detected in group 4 when compared with groups 1 and 3.

Subsequently, a gradual decrease in the level of TNF-α was observed in this group (4), where on day 14 after infection, the expression of TNF-α was the lowest.

Thus, 95% CI (confidence interval) in III and IV groups is between 2.4-4.0, which indicates an accurate assessment at $p\leq0.05$. The OR (odds ratio) was 0.9523107 between the use of a new drug based on Ganoderma lucidum and Alkhadaya and the severity of the pathological process in the lungs, $\chi 2$ (Wilconson criterion) is 0.93280714, U (Mann – Whiney criterion) is 0.94135082 at $p\leq0.05$.

Conclusions

The use of a new combination drug based on Ganoderma lucidum and Alkhadaya helps to regulate the levels of both pro-inflammatory and anti-inflammatory cytokines in coronavirus infection caused by SARS-CoV-2.

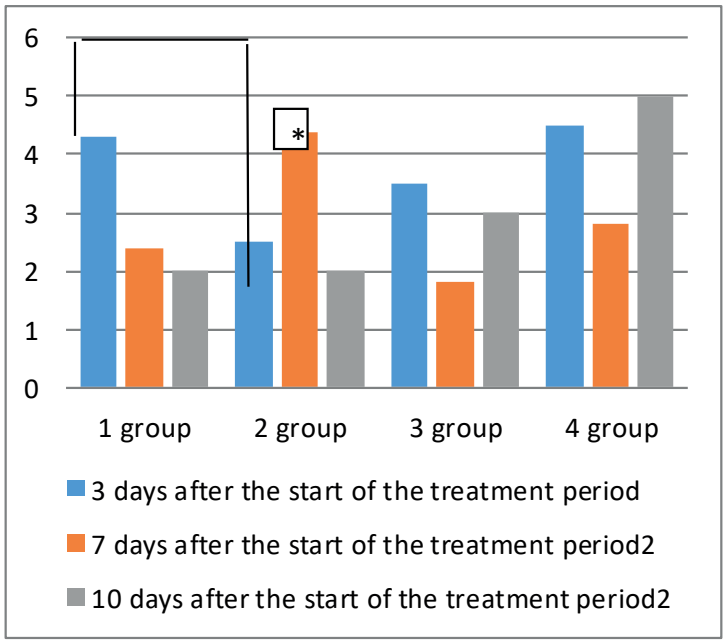

Fig. 1. IL-1β level in the study groups in coronavirus infection. * Mann – Whitney test.

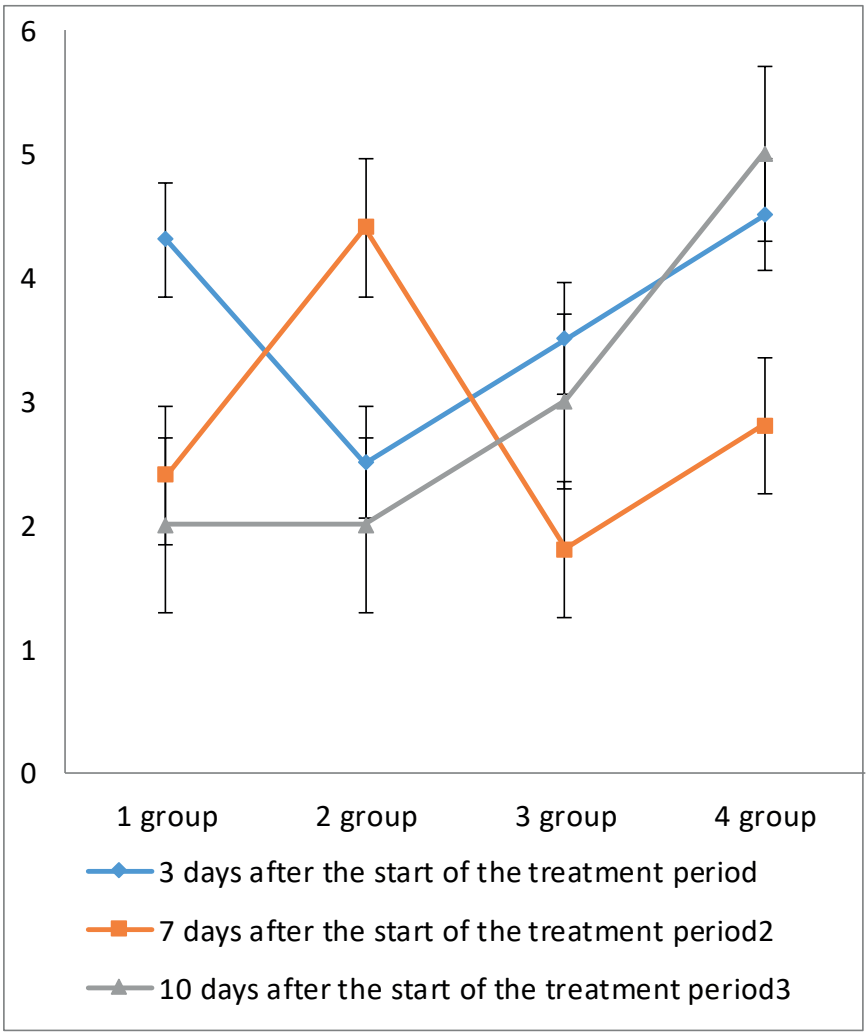

Fig. 2. IL-4 level in the study groups for coronavirus infection.

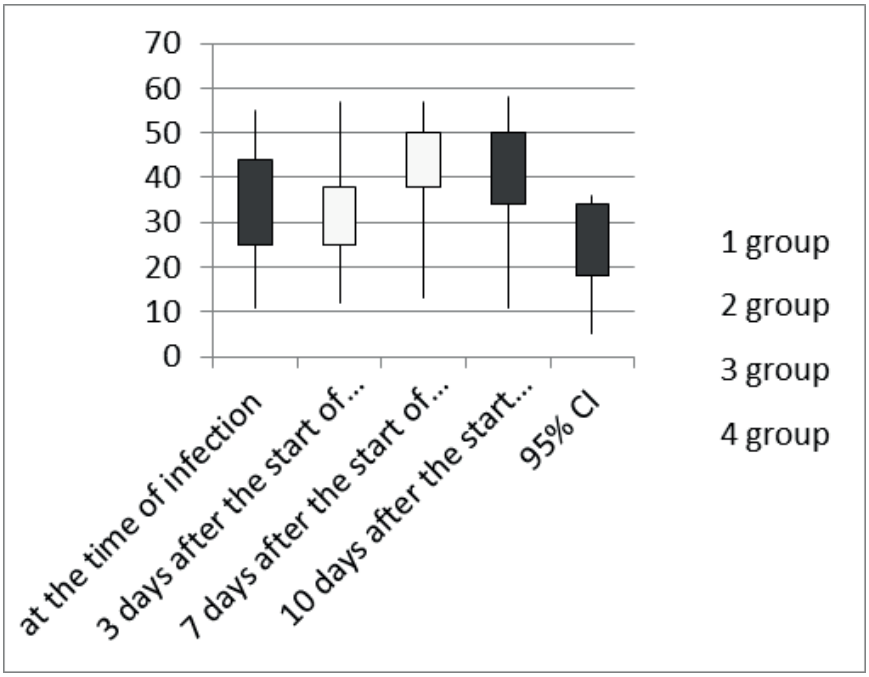

Fig. 3. Correlation relationship between the use of pro- and anti-inflammatory cytokines in coronavirus infection. CI – confidence interval.

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Уровень интерлейкинов в патогенезе коронавирусной инфекции (COVID-19) и влияние нового комбинированного препарата (G. lucidum и Alkhadaya) на течение и прогноз заболевания

Абилов П.М., Махкамова Ф.Т.

Цель: определение уровня интерлейкинов под воздействием нового комбинированного препарата на основе G. lucidum и Alkhadaya. **Материал и методы:** крысы были разделены на группы: 1-я – крысы с коронавирусной инфекцией с подтвержденным положительным ПЦР-тестом, леченные ивермектином в дозе 300 мг массы, 2-я – крысы с коронавирусной инфекцией, леченные байкалином в дозе 500 мг, 3-я – крысы с коронавирусной инфекцией, леченные молнупиравиром 25 мг/кг массы, 4-я – крысы с коронавирусной инфекцией, леченные новым препаратом на основе G. lucidum и Alkhadaya. **Результаты:** на 3-и сутки у животных всех групп уровень провоспалительного цитокина ИЛ-1β был достоверно выше контроля ($p<0,05$). Отношение шансов (OR) между применением нового препарата на основе Ganoderma lucidum и Alkhadaya и тяжестью патологического процесса в легких составило 0,9523107, $\chi 2$ (критерий Вилкоксона) – 0,93280714, U (критерий Манна – Уитни) – 0,94135082 при $p\leq0,05$. **Выводы:** применение нового комбинированного препарата на основе Ganoderma lucidum и Alkhadaya помогает корректировать уровни как провоспалительных, так и противовопаслительных цитокинов при коронавирусной инфекции, вызванной SARS-CoV-2.

Ключевые слова: коронавирус, Ganoderma lucidum, патогенез, коррекция, цитокины.

Koronavirus infektsiyasi (COVID-19) patogenezida interleykin darajasi va yangi kombinatsiyalangan preparatning (G. Lyusidum va Alxadaya) kasallikning kechishi va prognoziga ta’siri

Abilov P.M., Maxkamova F.T.

Maqsad: G. lucidum va Alxadaya asosidagi yangi kombinatsiyalangan dori ta’sirida interleykinlar darajasini aniqlash. **Material va usullar:** kalamushlar guruhlarga bo’lingan: 1-chi - tasdiqlangan PCR testi ijobiy bo’lgan koronavirus infektsiyasi bo’lgan kalamushlar, tana vazniga 300 mg dozada ivermektin bilan davolangan, 2-koronavirus infektsiyasi bo’lgan kalamushlar, 500 mg dozada bayalin bilan davolash qilingan, 3-chi - koronavirus / kg virusi bilan davolash qilingan kalamushlar vazni, 4-chi - G. lucidum va Alxadaya asosidagi yangi preparat bilan davolangan koronavirus infektsiyasi bo’lgan kalamushlar. **Natijalar:** 3-kuni barcha guruhlardagi hayvonlarda yallig’lanishga qarshi sitokin IL-1b darajasi nazoratga qaraganda ancha yuqori edi ($p<0,05$). Ganoderma Lucidum va Alkhadaya asosidagi yangi preparatni qo’llash va o’pkada patologik jarayonning og’irligi o’rtasidagi odds nisbati (OR) 0,9523107, ch2 (Wilcoxon testi) - 0,93280714, U (Mann – Whitney testi) - 0,95280, $p\ 13\leq5,02$.

Xulosa: Ganoderma lucidum va Alxadaya asosidagi yangi kombinatsiyalangan preparatni qo’llash SARS-CoV-2 keltirib chiqaradigan koronavirus infektsiyasida yallig’lanishga qarshi va yallig’lanishga qarshi sitokinlar darajasini tartibga solishga yordam beradi.

Kalit so’zlar: koronavirus, Ganoderma lucidum, patogenezi, tuzatish, sitokinlar.

Interleukin levels in the pathogenesis of coronavirus infection (COVID-19) and the effect of a new combination drug (G. lucidum and Alkhadaya) on the course and prognosis of the disease

Abilov P.M., Makhkamova F.T.

Objective: To determine the level of interleukins under the influence of a new combination drug based on G. lucidum and Alkhadaya. **Material and methods:** Rats were divided into groups: 1st - rats with coronavirus infection with a confirmed positive PCR test, treated with ivermectin at a dose of 300 mg of body weight, 2nd - rats with coronavirus infection, treated with baicalin at a dose of 500 mg, 3rd - rats with coronavirus infection, treated with molnupiravir 25 mg / kg of body weight, 4th - rats with coronavirus infection,

treated with a new drug based on G. lucidum and Alkhadaya. **Results:** On the 3rd day, the level of proinflammatory cytokine IL-1β in animals of all groups was significantly higher than in the control ($p<0.05$). The odds ratio (OR) between the use of a new drug based on Ganoderma lucidum and

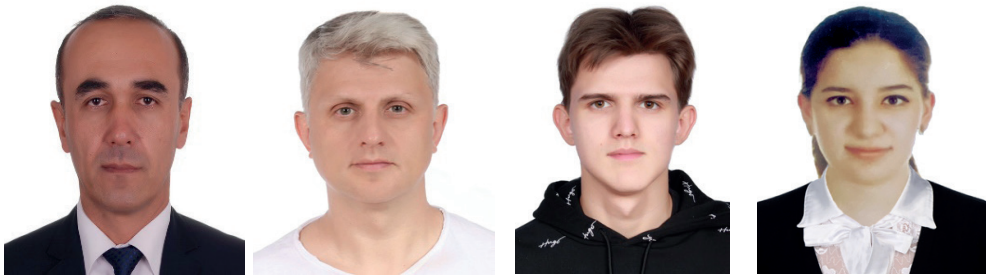
Alkhadaya and the severity of the pathological process in the lungs was 0.9523107, $\chi 2$ (Wilcoxon test) – 0.93280714, U (Mann – Whitney test) – 0.94135082 at $p \leq 0.05$. **Conclusions:** The use of a new combination drug based on Ganoderma lucidum and Alkhadaya helps to regulate the levels of both pro-inflammatory and anti-inflammatory cytokines in coronavirus infection caused by SARS-CoV-2.

Key words: coronavirus, Ganoderma lucidum, pathogenesis, correction, cytokines.

ТЕРАПЕВТИЧЕСКАЯ СТОМАТОЛОГИЯ

УДК: 616.311.2-002.2:618.2]-08:615.382-036.8

ТАП-ТЕРАПИИ ГИПЕРТРОФИРОВАННОГО ГИНГИВИТА БЕРЕМЕННЫХ ПРИ ПАТОЛОГИИ БЕРЕМЕННОСТИ: КЕЙС-СТАДИЯ.



Боймуродов Ш.А.[1], Ахмеров Р.Р.[2], Ахмеров Т.Р.[3], Гусева В.А.[4], Адилова А.Ш.[1]

[1]Ташкентский государственный медицинский университет, [2]Лаборатория Plasmolifting World GmbH Berlin B, [3]Российский университет Дружбы народов (Москва), [4]Клиника Молли (Санкт-Петербург)

Локальные инъекции ТАП применяется в стоматологической хирургии, ортопедии, ортодонтии, пародонтологии из-за эффективности противовоспалительных, регенеративных функций тромбоцитов. ТАП, стимулируя регенерацию повреждённых тканей, не провоцирует развитие онкологии. ТАП-терапия имеет доказанную эффективность в лечении заболеваний пародонта, но не используется при лечении гипертрофического гингивита беременных (ГГБ). Работы авторов по терапии гингивита, кроме одной, не включают исследований, посвященных ГГБ.

Лечение ГГБ – актуальная задача в Республике Узбекистан из-за умеренно высокого уровня рождаемости в стране, где традиционно поддерживается культ фертильности. Излишне высокая концентрация тромбоцитов вместо терапии оказывает неблагоприятное воздействие на жизнеспособность клеток. Исследования по ТАП-терапии при ГГБ нет. Российские исследователи считают беременность исключением для применения ТАП при лечении генерализированного пародонтита [3].

Методы исследования

Частота ГГБ колеблется от 30 до 100%. Есть мнение, что разброс цифр указывает лишь на то, что у женщин беременность протекает с осложнениями, т.к. при неосложненной беременности ГГ встречается всего у 20% беременных [1]. Для исследования мы исключали беременных с ВИЧ, COVID-19, гепатитом, новообразованиями, др. Нами были предусмотрены дополнительные исключения: многоплодная беременность; тяжелая патология беременности; железодефицитная анемия тяжелой формы (ниже 90 г/дл); низкое давление (ниже 100 мм рт. ст.); острые и хронические воспалительные заболевания (температура выше 37,2ºС); психические заболевания.