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Effect of kaempferol, amygdalin and methylprednisolone alone and in combination in induced cytokine storm in mice

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ABSTRACT

Cytokine storm can cause organ failure and even death in severe cases. There is ongoing research into developing drugs that can target cytokines and modulate the immune response to prevent or treat cytokine storm for that reason the present study aimed to evaluate the effect of kaempferol, amygdalin and methylprednisolone alone and in combination for their potential effectiveness in managing cytokine storm in a study including the collection of blood samples from groups included an apparently healthy, negative control, positive control and ten other groups of prophylaxis and treatment with methylprednisolone, kaempferol, amygdalin either alone or in combination to measure interleukin -1β, 6, 8 (IL-1β, 6, 8) and tumor necrosis factor- α (TNF-α) which demonstrated that in comparison with controls, the blood levels of IL-1, IL-6, IL-8, and TNF-α were significantly higher in the Lipopolysaccharide (LPS) group which decreased by using the studied drugs either alone or in combination for one hour before or after LPS induction which demonstrated that natural compounds such as amygdalin, and kaempferol have shown promise in reducing the levels of pro-inflammatory cytokines and may have therapeutic potential for the treatment of chronic inflammatory diseases.

Keywords: amygdalin, cytokine storm, kaempferol, methylprednisolone

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INTRODUCTION

Cytokine storm is a situation in which cytokines are released in excess in reaction to an infection or damage, resulting in an overactive immune response[1]. It is most commonly associated with severe cases of infections, such as coronavirus disease-2019 (COVID-19), H1N1 influenza virus, and is also seen in autoimmune disorders and certain cancers[2].

Interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α). are part of the cytokine network that has pro-inflammatory effects. Pro-inflammatory IL-1β is released in response to cell damage and lipopolysaccharide (LPS) metabolites from bacterial cell membranes[3]. An inflammatory cytokine with pleiotropic effects that promotes hematopoiesis, acute phase reactions, and particular immunological responses is IL-6. The greater death rate of COVID-19 has been related to IL-6[4]. One of the most important cytokines studied was TNF-α, which is involved in the cascade of inflammation and has a variety of intricate roles in the immune system[5,6].

There is currently no specific treatment for cytokine storm. Treatment is primarily supportive and may include measures to manage symptoms, such as oxygen therapy for respiratory distress, and medications to manage inflammation and fever[7,8]. However, certain drugs such as corticosteroids, tocilizumab, anakinra and baricitinib have been used to help regulate the immune response and reduce the risk of organ damage and other complications associated with cytokine storm but the use of these drugs is limited by their side effects[9-12]. In addition, some medications used to treat cytokine storm can increase the risk of blood clots, which can be a serious complication[13]. Immunosuppression drugs can increase the risk of infections and other complications which is a serious concern for immunocompromised patients[14].

For these reasons the scientific community need to development or find a new drug used for treatment of patient with cytokine storm with low or without side effect such as Kaempferol and Amygdalin. Kaempferol is one of the most commonly encountered aglycone flavonoids in the form of a glycoside which have been shown in numerous preclinical studies to have a variety of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, anti-diabetic, anti-osteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic activities[15].

Amygdalin is a plant glucoside from the Rosaceae family. The anti-fibrosis, anti-inflammatory, analgesic, auxiliary anticancer, immunoregulation, anti-atherosclerosis, anti-cardiac hypertrophy, anti-ulcer, and hypoglycemic prop-

erties of amygdalin have all received much research over the years. Additionally, it has the ability to cure neurological illnesses, stimulate ovulation, reduce endometriosis, and limit sperm hyaluronidase activity and motility[16].

The current work aimed to evaluate the efficacy of kaempferol, amygdalin, and methylprednisolone in treating cytokine storm by investigating their effect on the levels of IL-6, IL-18 and TNF-α in serum of Swiss Albino mice induced by lipopolysaccharide (LPS).

METHODOLOGY

A prospective control randomize experiment design was used in this study. Hangzhou Hyper Chemical Company (China) provided the amygdalin, methylprednisolone acetate, and kaempferol; Sigma Aldrich Chemical Company provided the LPS (USA). The dimethyl sulfoxide was given by Alpha Chemical (India) (DMSO). India's Edutek Co., Ltd. provided the formaldehyde. ELISA kits for IL-1β, IL-6, IL-8, and TNF were donated by SUN LONG Biological Technology Co. Ltd. in the USA.

Animals

In this investigation, 130 male Swiss albino mice weighing between 25 and 30g were used. They were purchased from the Center for Drug Control and Research. The Al-Nahrain University/College of Pharmacy animal ethics committee's guidance are used and care the experimental animals contains detailed instructions on how to handle and care for animals. Animals were kept in the Al-Nahrain University/College of Pharmacy's animal care facility for a 12-hour period in a light/dark cycle with frequent feedings of rodent food and water, the area was adequately ventilated and had fresh air.

Protocol for experimenting with cytokine storm models

To make the LPS solution, mix 10 mg of lyophilized LPS powder with 10 mL of normal saline in a sterile glass container, vortex mix it for 15 minutes, and then warm it in a water bath to thoroughly dissolve it before each use. The mice were randomly divided into thirteen groups of similar size (n=10).

- Group 1: (apparently healthy) ten male mice have not been received any treatment.
- Group 2: (negative control) ten males have been received 300 microliters of DMSO (<5%) intraperitoneally IP once daily for three days then received 0.13 ml IP equivalent to 5mg/kg of LPS and left for 48 hours.

- Group 3: (positive control) ten male mice have been received 0.13 ml single IP equivalent to 5mg/kg lipopolysaccharide (LPS) left for 48 hours.
- Group 4: (methylprednisolone prophylaxis group): ten male mice have been received methylprednisolone 1.25 ml IP from the stock solution equivalent to 50mg/kg once daily for three days then received 0.13 ml single IP equivalent to 5mg/kg of LPS left for 48 hours.
- Group 5: (kaempferol prophylaxis group): ten male mice receive 0.25 ml IP from the stock solution equivalent to 10mg/kg kaempferol once daily. for three days then received 0.13 ml single IP equivalent to 5mg/kg of LPS left for 48.
- Group 6: (amygdalin prophylaxis group) ten male mice have been received 0.08 ml equivalent to 3 mg/kg of amygdalin. IP once daily for three days then received 0.13 ml single IP equivalent to 5mg/kg of LPS left for 48 hours.
- Group 7: (kaempferol + methylprednisolone prophylaxis combination group); ten male mice receive 0.25 ml IP from the stock solution equivalent to 10 mg/kg kaempferol plus methylprednisolone 1.25 ml single IP from the stock solution equivalent to 50 mg/kg once daily for three days then received 0.13 ml single IP equivalent to 5 mg/kg of LPS after one hour left for 48 hours.
- Group 8: (amygdalin. + methylprednisolone prophylaxis combination group); ten male mice have been received 0.08 ml equivalent to 3 mg/kg of amygdalin plus, methylprednisolone 1.25 ml from the stock solution equivalent to 50 mg/kg IP once daily for three days then received 0.13 ml single IP equivalent to 5 mg/kg of LPS left for 48 hours.
- Group 9: (kaempferol treatment group); ten male mice have been received 0.13 ml microliters single IP equivalent to 5 mg/kg lipopolysaccharide (LPS) after one hour receive 0.25 ml IP from the stock solution equivalent to 10 mg/kg kaempferol. Twice daily for five days.
- Group 10: (amygdalin treatment group): ten male mice have been received 0.13 ml single IP equivalent to 5 mg/kg lipopolysaccharide (LPS) after one hour receive 0.075 ml IP from the stock solution equivalent to 3 mg/kg amygdalin. Twice daily for five days.
- Group 11: (kaempferol and methylprednisolone combination treatment group): ten male mice have been received 0.13 ml microliters single IP equivalent to 5 mg/kg lipopolysaccharide (LPS) after one hour receive 0.25

ml IP from the stock solution equivalent to 10 mg/kg kaempferol Plus methylprednisolone 1.25 ml single IP from the stock solution equivalent to 50 mg/kg Twice daily for five days.

- Group 12: (amygdalin + methylprednisolone combination treatment group): ten male mice have been received 0.13 ml single IP equivalent to 5mg/kg lipopolysaccharide (LPS) after one hour receive 0.075 ml IP from the stock solution equivalent to 3mg/kg amygdalin plus methylprednisolone 1.25 ml single IP from the stock solution equivalent to 50mg/kg twice daily for five days.
- Group 13: (methylprednisolone treatment group): ten male mice have been received 0.13 ml single IP equivalent to 5mg/kg lipopolysaccharide (LPS) after one hour receive methylprednisolone 1.25 ml IP from the stock solution equivalent to 50mg/kg. Twice daily for five days.
- Collect blood from all mice group from jugular vein under light anesthesia with chloroform after treatment period for each group, centrifuging for serum collection to quantitative measuring IL-1β, 6,8 and TNF-α by Elisa kit technique then scarified and collect liver, lung for histopathological examination.

Statistical analysis

The Social Sciences Software Statistics Package (SSPS) statistical software version (26) was used to collect, tabulate, and conduct all statistical analyses. The result was presented as Means SD. To compare across groups, a one-way analysis of variance (ANOVA) with post-hoc Tukey test. The level of significance was set at the p values, $p<0.01$ as significant, high significant and very high significant respectively[17].

RESULTS and DISCUSSION

The results showed that all of the tested compounds, including methylprednisolone, kaempferol, and amygdalin, were effective in preventing the elevation of IL-1β, IL-6, IL-8 and TNF-α levels when administered before or after LPS induction. Furthermore, the combined dosing of kaempferol, amygdalin, and methylprednisolone produced a synergistic effect in reducing the levels of IL-1β, IL-6, IL-8 and TNF-α levels (Figure 1-4, Table 1).

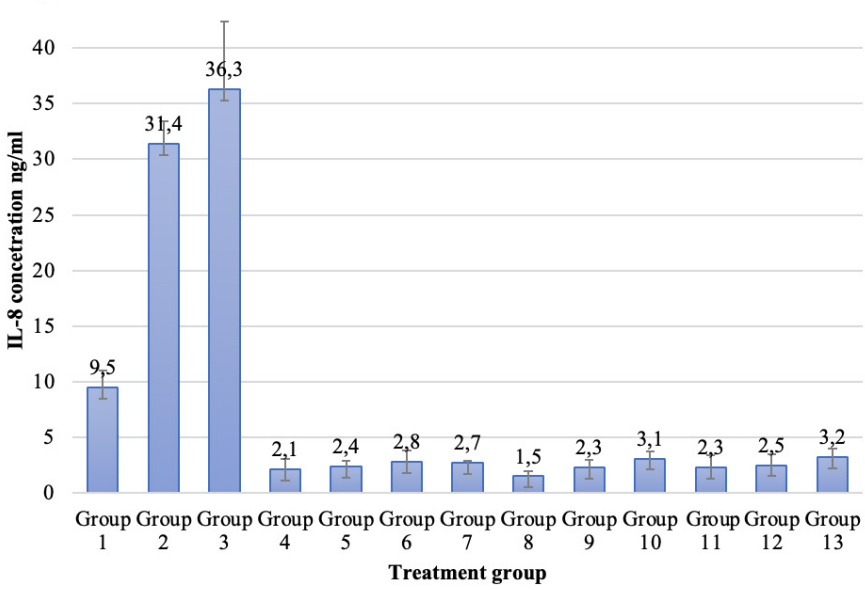

Figure 1. IL-8 level in all studied groups

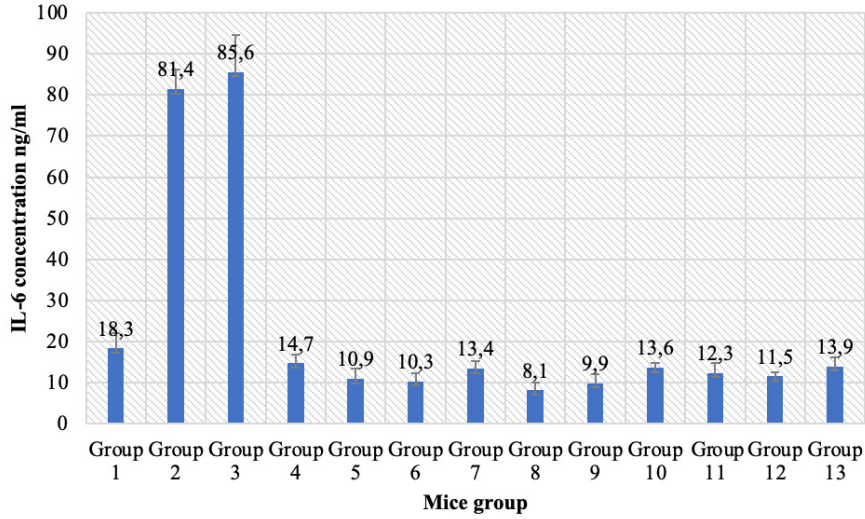

Figure 2. IL-6 level in all studied groups

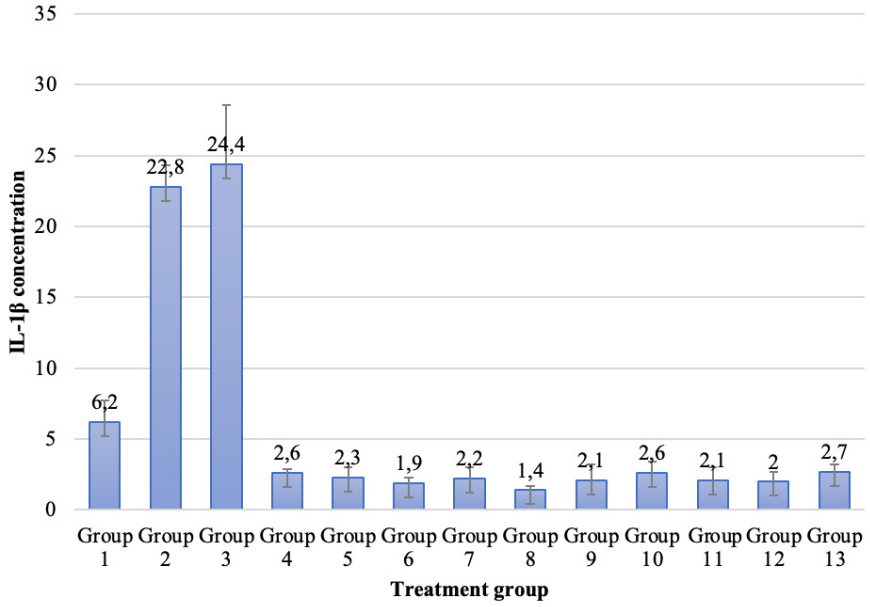

Figure 3. IL-1β level in studied groups

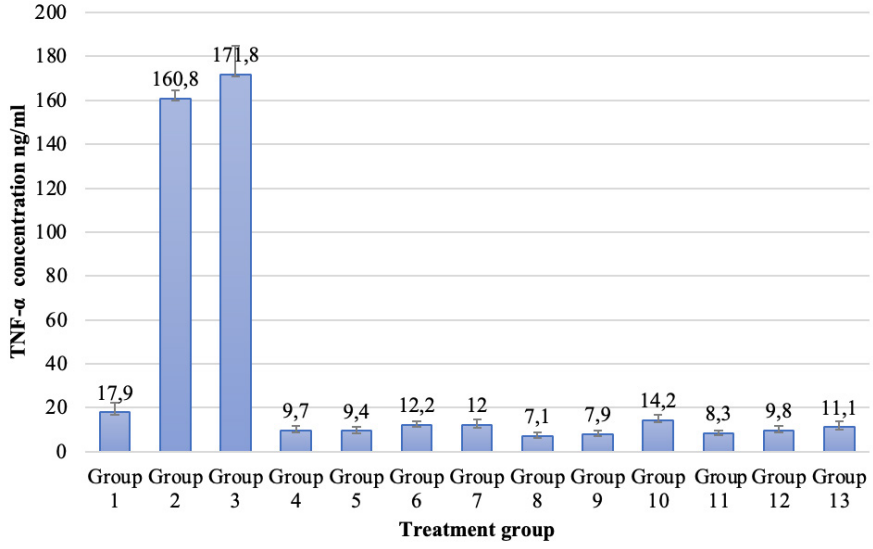

Figure 4. TNF-α level in studied groups

Table 1. Interleukin concentration in mice group after and before LPS induction

Group	IL-1β level as Mean ± SD in pg/ml	IL-6 level as Mean ± SD in ng/ml	IL-8 level as Mean ± SD in ng/ml	TNF-α level as Mean ± SD in ng/ml
Group 1 (Healthy)	6.2 ± 1.5ab	18.3 ± 3.8bb	9.5 ± 1.5ab	17.9 ± 4.4bb
Group 2 Negative Control (Dmso)	22.8 ± 1.5bb	81.4 ± 4.9a	31.4 ± 2.0bc	160.8 ± 3.9 dd
Group 3 Positive Control (Lps)	24.4 ± 4.2bb	85.6 ± 8.9a	36.3 ± 6.1bc	171.8 ± 13.1dd
Group 4 (Methylprednisolone Prophylaxis)	2.6 ± 0.3cc	14.7 ± 2.1bd	2.1 ± 1.0cc	9.7 ± 2.0ab
Group 5 (Kaempferol Prophylaxis)	2.3 ± 0.7cc	10.9 ± 2.5ab	2.4 ± 0.5cc	9.4 ± 1.8ab
Group 6 (Amygdalin Prophylaxis)	1.9 ± 0.4cc	10.3 ± 2.1ab	2.8 ± 1.0cc	12.2 ± 1.7ab
Group 7 (Kaempferol + Methylprednisolone Prophylaxis)	2.2 ± 0.8cc	13.4 ± 1.9bd	2.7 ± 0.2cc	12.0 ± 2.8ab
Group 8 (Amygdalin+ Methylprednisolone Prophylaxis)	1.4 ± 0.3cc	8.1 ± 1.9ab	1.5 ± 0.5cc	7.1 ± 1.5ab
Group 9 (Kaempferol Treatment)	2.1 ± 1.1cc	9.9 ± 2.1ab	2.3 ± 0.7cc	7.9 ± 1.6ab
Group 10 (Amygdalin Treatment)	2.6 ± 0.8cc	13.6 ± 1.1bd	3.1 ± 0.6cc	14.2 ± 2.4ab
Group 11 (Kaempferol+ Methylprednisolon Treatment)	2.1 ± 0.9cc	12.3 ± 2.4bd	2.3 ± 1.1cc	8.3 ± 1.3ab
Group 12 (Amygdalin + Methylprednisolon Treatment)	2.0 ± 0.7cc	11.5 ± 1.1bd	2.5 ± 1.0cc	9.8 ± 2.1ab
Group13 (Methylprednisolone Treatment)	2.7 ± 0.5cc	13.9 ± 2.3bd	3.2 ± 0.8ccc	11.1 ± 2.6Aa

Group 4-8 administration of compounds before receiving LPS, group 9-13 administration of treatment compounds after cytokine induction by LPS. similar later not have significant difference at $p<0.01$ by using LSD. different later have significant difference at $p<0.01$ by using LSD.

The body's immunological reaction to an infection or damage involves inflammation, which is a critical step. On the other hand, persistent inflammation has been linked to a number of illnesses, including as cancer, autoimmune disorders, and cardiovascular conditions. Pro-inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α are important in the beginning and development of inflammation[18,19]. Thus, inhibition of these cytokines can be a therapeutic strategy for various inflammatory diseases. In recent years, natural compounds have gained attention as potential anti-inflammatory agents due to their safety profile and effectiveness[20].

The study aimed to assess the effect of various compounds on the levels of interleukin- IL-1β, IL-6, IL-8 and TNF-α levels in serum samples collected from different groups of mice. The serum samples were collected from healthy mice (Group 1), mice treated with DMSO (Group 2), and mice treated with LPS (Group 3). Groups 4 to 13 were pre-treated or treated with various compounds before or after LPS administration. The IL-1β, IL-6, IL-8 and TNF-α levels were quantitatively assessed using enzyme-linked immunosorbent assay (ELISA) kits, and the findings were statistically analyzed.

Kaempferol is a flavonoid found in various plant-based foods such as tea, broccoli, and berries. The production of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α has been shown to be inhibited by kaempferol, giving rise to its anti-inflammatory effects[21]. The findings shown that Kaempferol substantially and dose-dependently decreased the levels of IL-1β, IL-6, and TNF-α which is agreed with a study conducted by Chen et al. (2019) who demonstrated that kaempferol treatment significantly reduced the levels of IL-1β, IL-6, and TNF-α in LPS-induced RAW264.7 macrophages. Furthermore, kaempferol treatment also reported to suppress the activation of NF-κB and MAPK signaling pathways, which are critical pathways involved in the regulation of inflammatory responses[22].

According to reports, amygdalin has anti-inflammatory characteristics by preventing the formation of cytokines that promote inflammation, such as IL-1β, IL-6, and TNF-α[16,23] which is consistent with the results obtained in the current study. *In vivo* study conducted by Li et al. (2023) also demonstrated that amygdalin treatment group significantly reduced the expression of IL-1β, IL-6, and TNF-α after lipopolysaccharide (LPS) induction[24]. It was reported that Amygdalin significantly reduced the levels of IL-1β, IL-6, and TNF-α in a dose-dependent manner. Amygdalin significantly inhibited the production of IL-6 and TNF-α in LPS-stimulated macrophages. The authors suggested that the anti-inflammatory effect of amygdalin might be mediated through the inhibition of NF-κB and MAPK signaling pathways[25].

Synthetic glucocorticoids like methylprednisolone are frequently used to treat inflammation and inhibit the immune system. By inhibiting the synthesis of pro-inflammatory cytokines such IL-1β, IL-6, IL-8, and TNF-α, methylprednisolone reduces inflammation[26]. The methylprednisolone treatment significantly reduced the levels of IL-1β, IL-6, and TNF-α in a rat model of acute lung injury. Methylprednisolone treatment also attenuated the histological damage and improved the respiratory function in the rat model[27].

The results of the present study are consistent with previous research that has demonstrated the anti-inflammatory properties of kaempferol, amygdalin, and methylprednisolone. Kaempferol has been shown to inhibit the production of pro-inflammatory cytokines such as IL-1β and TNF-α in various cell lines[28]. Similarly, amygdalin has been found to suppress the production of inflammatory mediators in macrophages[24], while methylprednisolone is a well-known anti-inflammatory agent that is frequently used to treat inflammatory conditions such as asthma and rheumatoid arthritis[29].

Interestingly, the present study also suggests that the combination of these compounds produces a synergistic effect in reducing IL-1β levels. This finding is consistent with previous studies that have demonstrated the benefits of combining natural compounds with synthetic drugs to enhance their therapeutic effects[30]. For example, mixing between dexamethasone and quercetin may have a synergistic impact on cytokine storm inhibition. Dexamethasone suppresses the immune system largely, but quercetin can target particular inflammatory pathways and alter cytokine production in covid 19 patient[31]. Moreover, the present study highlights the potential use of these compounds as a combination therapy in the treatment of inflammatory disorders.

Natural substances including amygdalin and kaempferol have been shown to have anti-inflammatory characteristics by lowering the levels of pro-inflammatory cytokines like IL-1β, IL-6, IL-8, and TNF-. These substances could be able to cure inflammatory illnesses that are chronically present. To assess these substances' effectiveness and safety in people, more research is required.

STATEMENT OF ETHICS

The study received approval from the "Institute Review Board (IRB) of Al-Nahrain University/College of Medicine" in January 2022 (58/2022).

CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared by the authors.

AUTHOR CONTRIBUTIONS

Design – Gatea FK; Acquisition of data – Obaid SH; Analysis of data – Obaid SH; Drafting of the manuscript – Obaid SH; Critical revision of the manuscript – Obaid SH, Gatea FK; Statistical analysis – Obaid SH; Technical or financial support – Obaid SH, Gatea FK; supervision – Gatea FK.

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