Impact of Aqueous Extract of Ginger and Chamomile Plant and Some Antihistamines in the Treatment of Drug-Allergy Induced in White Rats, a Physiological and Immunological Study

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Abstract

This study was conducted at the Animal House of the College of Veterinary Medicine/University of Tikrit to know the role of chamomile and ginger aqueous extract in the treatment of induced pharmacological sensitization in white rats and compare it with the drug Histidine. The study included 36 white rats, and they were divided into four groups, the control group included 9 animals whose diet was normal (feed and distilled water), and the second group included 9 animals that were dosed with amoxicillin at a concentration of 1 ml / kg, the third group included 9 animals that were dosed with sulfamethoxazole at a concentration of 1 ml / kg, the fourth group included 9 animals that were dosed with aspirin at a concentration of 1 ml / kg, and after infection and the appearance of allergy symptoms on the animals, the three affected groups of rats were treated with aqueous extract of chamomile plant at a concentration of 2 ml / kg, and aqueous extract of ginger at a concentration of 1 ml / kg, Histidine, at a concentration of 1 ml / kg, the results showed a significant increase in the activity of interleukin-4 IL-4 and tumor necrosis factor-alpha-TNF-α, ($p<0.05$) in the amoxicillin group, sulfamethoxazole and aspirin group compared to the healthy control group, the results also showed a significant decrease in the activity of interleukin-4 and tumor necrosis factor-alpha-TNF-α in the treated groups treated with aqueous extract of ginger and chamomile and the histidine group compared to the sensitive groups. We conclude from this study that medicinal plants such as ginger and chamomile have anti-allergic and anti-inflammatory therapeutic properties due to the fact that they contain effective compounds such as phenols, flavonoids, and glycosides. Histidine is also one of the antihistamines of first generation that works by binding to H1 receptors in various cells of the body, thus preventing the release of histamine from mast cells and basophils, which is responsible for the occurrence of allergic reactions in the body and thus inhibits allergic reactions.

Keywords: Drug Allergy, IL-4, Ginger, TNF-α, Chamomile.

Introduction

Medicinal plants are one of the most important treatments that scientists and researchers are interested in in the field of drug manufacturing because of their importance in treating diseases and maintaining human health, and it is preferable to use them because they are free of side effects compared to the use of medicinal drugs[1]. Ginger is an important medicinal plant that grows in hot regions, which contains volatile oil with a pungent smell and a pungent taste, it contains major compounds, including Gingerols, Shogaols, which are used as anti-allergic and anti-inflammatory treatments, including allergic inflammatory diseases such as asthma, arthritis, colon, migraine, and anti-thrombotic [2].

The chamomile plant is of great importance, as its extracts are included in the components of medical soap to improve the appearance of the skin and protect it from rashes and the types of allergies that affect it, its extracts are also used in the treatment of various skin diseases, it is also considered anti-allergic and anti-inflammatory because it contains active compounds such as tannin, azulene, isobutanol, isoamyl, rutin and quercetin[3].

A drug allergy is one of the important and common cases of allergy, which is a reaction caused by an overactive immune system to a prescription or over-the-counter drug, or the wrong use of treatment, or any herbal drug capable of stimulating an allergy [4], the immune system produces proteins called antibodies that protect the body from unwanted foreign bodies that invade the body and cause diseases and infections such as viruses and bacteria, when someone is allergic to a particular substance, their immune system produces antibodies that identify the agent that caused the allergy and treat it as a harmful element, although it is not, which leads to the release of histamine, which causes allergy symptoms[5].

Drug reactions are common in daily clinical practice, affecting 15-25% of patients, and serious allergic reactions occur in 7-13% of patients [6], adverse drug reactions are classified as either predictable reactions that may occur in any person, called type A reactions, or unpredictable reactions that occur in susceptible people, called type B reactions, predictable reactions are the

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most common type of ADR reactions and are usually dose-dependent and related to known drug actions (such as drug side effects, overdose, drug interactions), while unpredictable type B drug reactions are not usually related to the pharmacological actions of the drug, drug sensitivity is due to unpredictable type B drug ADR reactions, which include a group of immune hypersensitivity reactions mediated by different mechanisms to varying degrees [7], the sensitivity of the drug does not affect the life of the patient only, but also in the delay in responding to treatment, which leads to death, and therefore an accurate diagnosis must be made by knowing the suspected drug and the exact date of giving the treatment[8].

Materials and Working Methods

Study samples

This study was conducted in the animal house of the College of Veterinary Medicine / Tikrit University for the period from March 31, 2021 to May 15, 2021. The study included 36 white female rats, their ages ranged from (18-16) weeks and weighed (260-200) grams.

The study groups were divided into four groups as follows:

1- **Control group:** This group included 9 animals whose diet was natural (feed and distilled water).

2- **Amoxicillin group:** This group included 9 animals that were dosed with amoxicillin at a concentration of 1 ml/kg at a rate of one dose per day for 30 days, after an allergic reaction, the group was divided into three groups, each group included 3 animals that were treated at a rate of one daily dose with aqueous extract of chamomile at a concentration of 2 ml / kg, aqueous extract of ginger at a concentration of 1 ml / kg, and histidine at a concentration of 1 ml / kg for 15 days.

3- **Aspirin group:** This group included 9 animals that were dosed with aspirin at a concentration of 1 ml/kg at a rate of one dose per day for 30 days, after an allergic reaction, the group was divided into three groups, each group included 3 animals that were treated at a rate of one daily dose with aqueous extract of chamomile at a concentration of 2 ml / kg, aqueous extract of ginger at a concentration of 1 ml / kg, and histidine at a concentration of 1 ml / kg for 15 days.

4- **Sulfamethoxazole group:** This group included 9 animals that were dosed with sulfamethoxazole at a concentration of 1 ml/kg at a rate of one dose per day for 30 days, after an allergic reaction, the group was divided into three groups, each group included 3 animals that were treated at a rate of one daily dose with aqueous extract of chamomile at a concentration of 2 ml / kg, aqueous extract of ginger at a concentration of 1 ml / kg, and histidine at a concentration of 1 ml / kg for 15 days.

Sample collection

Blood samples were collected after the end of the experiment. Animals were starved for 12 hours and then anesthetized with ketamine and Xylazine at doses of 5-35 mg/kg of body weight by intramuscular injection[9]. Then, blood samples were drawn from the heart directly by a heart stab method, and the blood was placed in plastic tubes free of anticoagulant and left for 15 minutes at room temperature until the blood clotted, then the tubes were placed in a centrifuge at 3000 rpm for 15 minutes in order to obtain the blood serum, the serum was kept by freezing at a temperature of -20 until the required tests were performed.

Measurement of serum IL-4 concentration

The concentration of IL-4 in serum was determined by ELIZA by Enzyme-Linked Immunosorbent Assay using ready-made assay kit (kit) provided by Sunlong,2021.

Estimation of TNF-α concentration in serum:

The efficacy of tumor necrosis factor alpha-α TNF-α was determined by ELIZA by Enzyme-Linked Immunosorbent Assay using ready-made assay kit supplied by Sunlong, 2021[10].

Measurement of serum AST concentration

The AST concentration in serum was determined by using a ready-made (kit) analysis kit from Biolabo Company[11].

Measurement of serum ALT concentration

The serum ALT concentration was determined using a ready-made kit (kit) from Biolabo Company[12].

Statistical Analysis

The statistical results were analyzed based on the One-Way Analysis of Variance using the (SAS) program, and the arithmetic means of the coefficients were tested using the Dunkin' polynomial test with a significant level ($p<0.05$)[13].

Results and Discussion

Concentration of IL-4 and TNF-α in serum

The results shown in Figure (1) indicate a significant increase at the probability level ($p<0.05$) in the concentration of interleukin-4 IL-4 in the serum of rats for groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, the results also showed a significant decrease at the probability level ($P < 0.05$) in the concentration of interleukin-4 IL-4 in the serum of rats after treatment with aqueous extracts of ginger, chamomile and histidine group compared to its concentration before treatment.

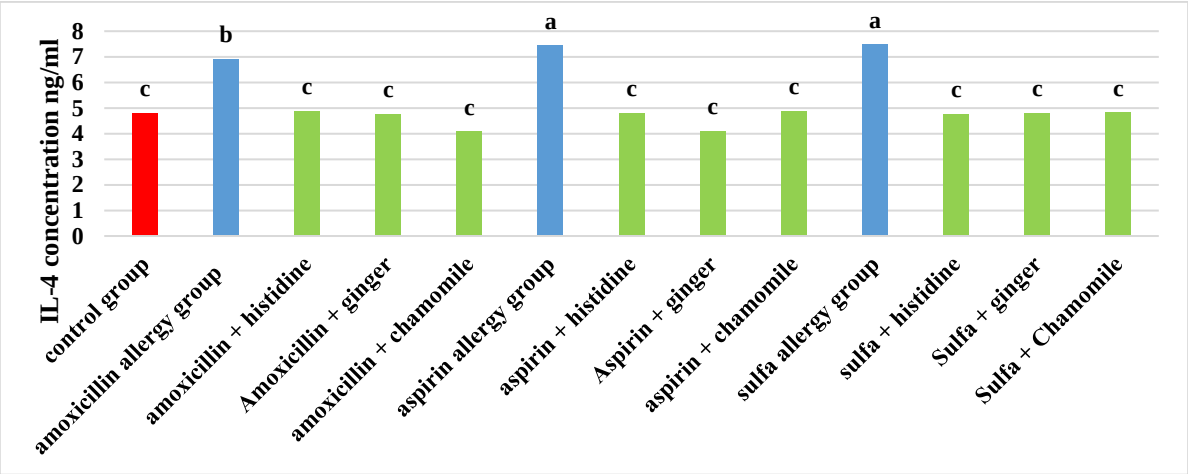

Figure (1) Interleukin IL-4 concentration in the studied groups (different letters mean a significant difference at the level of significance (p<0.05)).

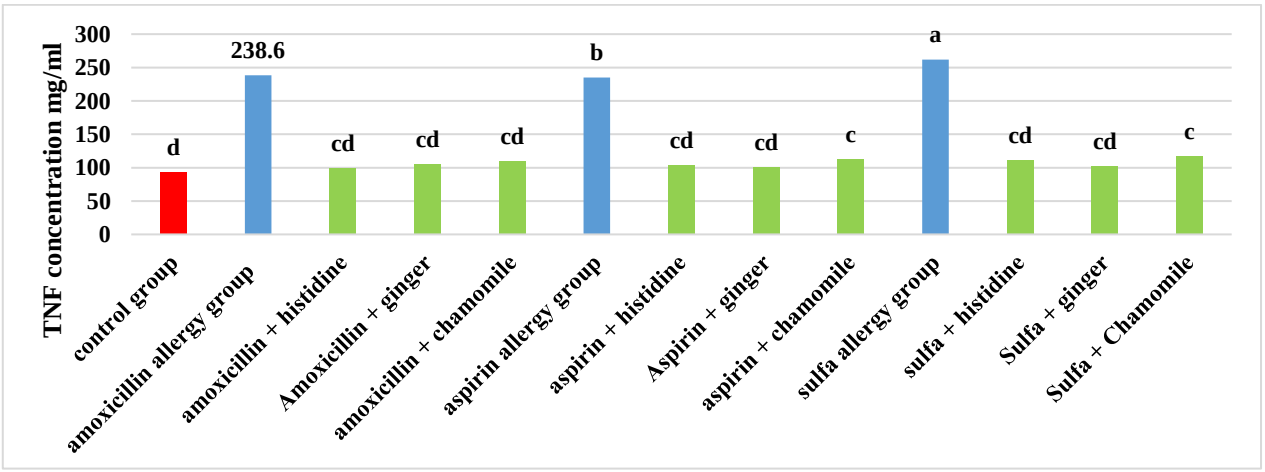

Figure (2) The TNF-α concentration in the studied samples (different letters mean a significant difference at the level of significance (p<0.05)

The results shown in Figure (2) indicate that there is a significant increase at the probability level (p<0.05) in tumor necrosis factor alpha-α TNF-α concentration in the serum of rats for groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, the results also showed a significant decrease at the probability level (P < 0.05) in tumor necrosis factor alpha-α TNF-α concentration in the serum of rats after treatment with aqueous extracts of ginger and chamomile, and histidine group compared to their concentration before treatment.

The results of the current study showed a significant increase in Concentration of interleukin-4 IL-4 and tumor necrosis factor-alpha-TNF-α in the serum of rats in the groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, this increase can be attributed to the occurrence of the inflammatory process associated with the occurrence of allergies in the body, allergic inflammation is divided into two phases: the sensitization phase is the phase of activation and production of IgE from basophils and mast cells after exposure to allergens[14] [15]. Mast cells are widely distributed throughout the mucosal and connective tissues and are the main effectors of allergic inflammation mediated by specific IgE that binds to high-affinity receptors (FcεRI) expressed on the surface of basophils and mast cells[16].

Re-exposure to the same allergen leads to the cross-linking of IgE molecules bound to FcεRI and the release of signals that ultimately lead to elevated calcium levels within mast cells, as for the second phase, it is the clinical phase, during which symptoms appear after exposure to the allergen, the symptomatic phase is also divided into: the early stage, which involves the decomposition of granules from mast cells and the release of various inflammatory mediators such as histamine, leukotriene and prostaglandin D2 (PGD2) and the release of inflammatory cytokines such as IL-1, IL-3, IL-4.IL-5, IL-13, release of tumor necrosis factor-alpha (TNF-α) [17], and the late stage, which is associated with an increase in inflammatory cells resulting from repeated cytokine secretion[18].

Hexosaminidase is stored in the secretory granules of mast cells and released from the same cells during an immune response, its release stimulates cross-linking of IgE with FcεRI, this explains the high concentrations of interleukins IL-1, IL-4, TNF-α and C-reactive protein (CRP) in the serum of the three sensitivity groups in this study. TNF is a key regulator of pro-inflammatory cytokines that causes inflammation and the development of chronic inflammatory diseases[19].

The decrease in the concentrations of IL-4, TNF-α immunomodulators in the blood serum of the histidine group is due to the fact that this drug is an antihistamine that acts as an antagonist of the first-generation histamine H-1 receptors, which is fast and long-acting and has an effect on inflammatory cells, it acts as an anti-inflammatory drug and studies have shown that H-1 receptor antagonists have an effect on the allergic inflammatory response[20]. Also, the results of the treated groups treated with plant extracts of ginger and chamomile showed a significant decrease in the concentration of the immunomodulators (TNF-α, IL-4,) compared to the sensitive groups (amoxicillin group, aspirin group and sulfa group), and this decrease can be attributed to their containing compounds Biologically active flavonoids, phenols, alkaloids and glycosides, these compounds possess inhibitory, anti-inflammatory[21], anti-allergic[22] and antioxidant[23] properties.

The aqueous extracts of ginger and chamomile plant have high anti-allergic properties through the ability of their active compounds to inhibit hexosaminidase and thus reduce the release of inflammatory and allergic mediators[24].

The concentration of liver enzymes AST, ALT in the blood serum

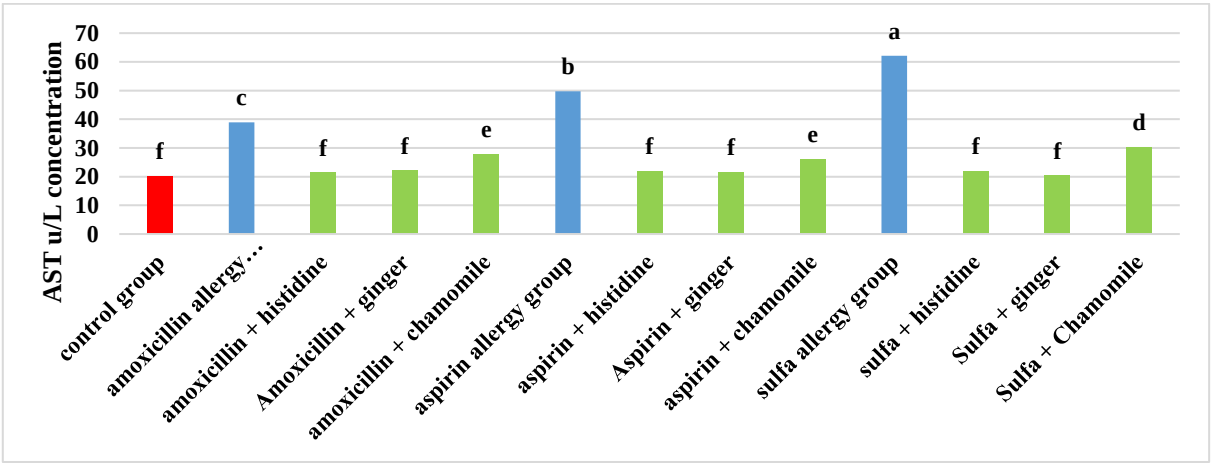

Figure (3) the concentration of AST enzyme in the studied groups (different letters mean there is a significant difference at the level of significance (p<0.05))

The results shown in Figure (3) indicate a significant increase at the probability level (p<0.05) in AST enzyme concentration in the blood serum of rats for groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, the results also showed a significant decrease at the probability level (P < 0.05) in AST enzyme concentration in the blood serum of rats after treatment with aqueous extracts of ginger, chamomile, and histidine group compared to its concentration before treatment.

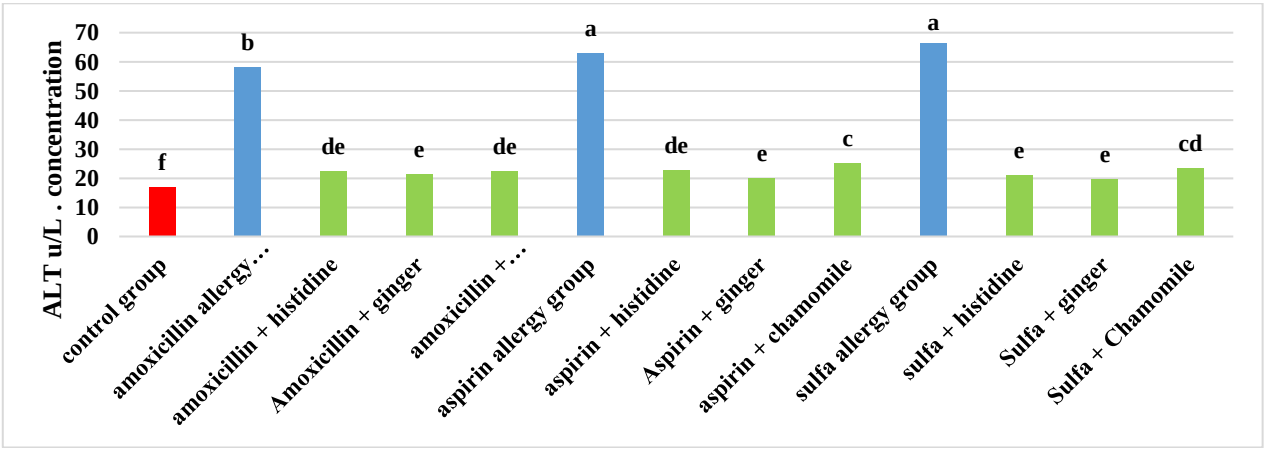

Figure (4) ALT enzyme concentration in the studied groups (different letters mean a significant difference at the level of significance (p<0.05)).

The results shown in Figure (4) indicate a significant increase at the probability level (p<0.05) in the concentration of the enzyme, ALT in the serum of rats for the groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, the results also showed a significant decrease at the probability level (P < 0.05) in the concentration of the enzyme, ALT in the serum of rats after treatment with aqueous extracts of ginger, chamomile, and histidine group compared to its concentration before treatment.

The high concentration of liver enzymes AST, ALT in the allergic groups (amoxicillin group, aspirin and sulfa) can be attributed to a defect in the work of the liver, the body recognizes almost all medicines as foreign substances, and subject it to various chemical

processes are metabolic processes to make it suitable for disposal, although all body tissues have some ability to metabolize chemicals,, however, the smooth endoplasmic reticulum in the liver is the basis for drug metabolism, it is the metabolic clearing house for each of the endogenous chemicals such as (proteins, fatty acids, cholesterol and steroid hormones) and exogenous substances such as (drugs and alcohol)[25], 75% of the blood is transported to the liver via the digestive tract, then the spleen, and then the hepatic portal vein, the metabolism of the drug is divided into two phases, which include the reactions of the first phase, oxidation, reduction and hydrolysis, thus increasing the solubility of the drug in water, which can generate more chemically active and potentially toxic metabolites, as for the second stage, after the metabolites of the drugs have become in the cytosol, it involves conjugation with the endogenous compounds through the hepatic transfer enzymes, the group of enzymes in the endoplasmic reticulum known as cytochrome p-450 is the most important family of drug metabolism in the liver, Cytochrome p-450 is a terminal oxidase component of the electron transport chain, liver dysfunction caused by drug sensitivity causes damage to liver cells and organelles, producing inflammatory mediators such as inflammatory cytokines, leukotrienes and TNF-alpha damage to mitochondria, which are energy-producing houses, in addition to producing a large amount of oxidants that in turn damage liver cells, the activation of some enzymes in the cytochrome p-450 system such as CYP2E1 also leads to oxidative stress that results in free radicals and reactive oxygen species (ROS) such as hydroxyl radicals, lipid oxyl or peroxyl radicals and oxygen, the singular O and nitrogen oxides NO, all of these atoms are called free radicals FR, the oxidation of lipids leads to its production, and these radicals cause cell damage and release marker enzymes in the liver and kidneys as a result of damage to the cellular plasma membrane, a variety of enzymes in the cytosol are released into the bloodstream, so elevated levels in the serum are a sign of hepatic and renal cellular damage[26].

The results showed a significant decrease in the activity of liver enzymes (AST, ALT) in the histidine group, compared to the three affected groups, this decrease can be attributed to the fact that this drug acts as an antihistamine, which has the main role in stimulating inflammatory responses and the secretion of many inflammatory mediators such as cytokines, leukotrienes and tumor necrosis factor, in addition to releasing reactive oxygen species and free radicals that destroy body tissues, it suppresses histamine receptors and thus acts as an anti-allergic and anti-inflammatory[27].

The results also showed a significant decrease in the aqueous extracts of ginger and chamomile groups in the activity of liver enzymes (AST, ALT) compared to the infected groups (amoxicillin group, aspirin group and sulfa group), this decrease can be attributed to the healing properties of ginger and chamomile plants, phenolic compounds, flavonoids, glycosides, and alkaloids are powerful anti-inflammatory and powerful antioxidants, as they are able to scavenge and inhibit free radicals such as nitric oxides, hydroxyl radicals and single oxygen groups, they act as natural antioxidants that reduce inflammatory factors such as inflammatory cytokines and tumor necrosis factor-alpha, thus contributing to reducing tissue damage[28].

Acharya and his group suggested that the presence of the reductants matched the reductive powers of the extracts by violating the free radical chain, followed by the provision of a hydrogen atom[29], the ability to reduce depends on the presence of free radical molecules in the extract or compound, which exerts a scavenging activity by giving a hydrogen atom and inhibiting the free radical chain in the system[30], the naturally occurring plant phenol contributes to beneficial health properties by reducing free radical oxygen[31].

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