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# DRUG ALLERGY TREATMENT INDUCED IN WHITE RATS MEDIATED BY THE AQUEOUS EXTRACT OF CHAMOMILE PLANT, GINGER AND HISTIDINE DRUG IMMUNOLOGICAL AND PHYSIOLOGICAL 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 IgE and IgG immunoglobulins ($p<0.05$) in the amoxicillin group, sulfamethoxazole and aspirin group, in comparison with the healthy control group, the results also showed a significant decrease in the activity of IgG and IgE immunoglobulins in groups treated with aqueous extract of ginger and chamomile and Histidine group compared to the allergy 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, IgE, Ginger, IgG, Histidine.

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## Introduction

The roots of the term or concept of allergy are closely related with immunology and pharmacology, and with the advancement of scientific technology around the study of drug allergy, a wide range of research methodologies have been applied in humans in addition to animal models, using chemically diverse pharmacological agents administered to patients, and this diversity continues with the launch of each new drug.

There is always the possibility of adverse reactions to drugs given to patients, abnormal reactions of the immune system to a drug are called a drug allergy, which is different from the known potential side effects of the drug listed on the drug label, and it also differs from drug toxicity that results from taking an overdose of the drug. The diversity of chemical structures of drugs in addition to their pharmacological action sometimes leads to the emergence of a negative reaction from the body towards these drugs, the drug allergy is one of the types of adverse drug reaction (ADR), which is defined as any harmful drug reaction or unintended reaction to a drug taken. Doses used for treatment, diagnosis, or prevention. Drug reactions are common in daily clinical practice, affecting 15-25% of patients, and serious allergic reactions occur in 7-13% of patients. Adverse drug reactions are classified as either predictable reactions that can occur in any person, called type A reactions, or unexpected reactions that occur in susceptible people, called type B reactions. Predictable reactions are the most common type of ADR reactions and are usually dose-dependent and related to known drug actions (such as drug side effects, overdose, and drug interactions). While unpredictable type B drug reactions are not usually related to the pharmacological actions of the drug, drug allergy is due to unpredictable type B drug ADR reactions, which include a group of immune hypersensitivity reactions mediated by different mechanisms to varying degrees. The drug allergy does not only affect the patient's life, but also delays the response to treatment, which leads to death, and therefore an accurate diagnosis is required by knowing the suspected drug, the exact date of giving treatment, physical examination, in addition to skin tests, and the most effective procedure is to stop treatment for the patient or change the drug. Hypersensitivity to drugs is treated with topical corticosteroids and oral antihistamines, and in severe cases, systemic corticosteroids are used, or treatment may be with an injection of epinephrine.

## 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

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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. 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 IgE concentration**

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

**Measurement of serum IgG concentration**

The efficacy of serum IgG immunoglobulin was determined by ELIZA by Enzyme-Linked Immunosorbent Assay using ready-made assay kit supplied by Sunlong, 2021.

**Measurement of serum creatinine concentration**

The serum creatinine concentration was estimated using a ready-made (kit) analysis kit from Biolabo Company.

**Measurement of serum albumin concentration**

The serum albumin concentration was estimated using a ready-made (kit) from Biolabo Company.

**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 ($p<0.05$).

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**Results and Discussion:**

**Concentration of IgE and IgG in the blood serum:**

The results shown in Figure (1) indicate a significant increase at the probability level ($p<0.05$) in the concentration of IgE 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 IgE in the serum of rats after treatment with aqueous extracts of ginger, chamomile and histidine group compared to its concentration before treatment.

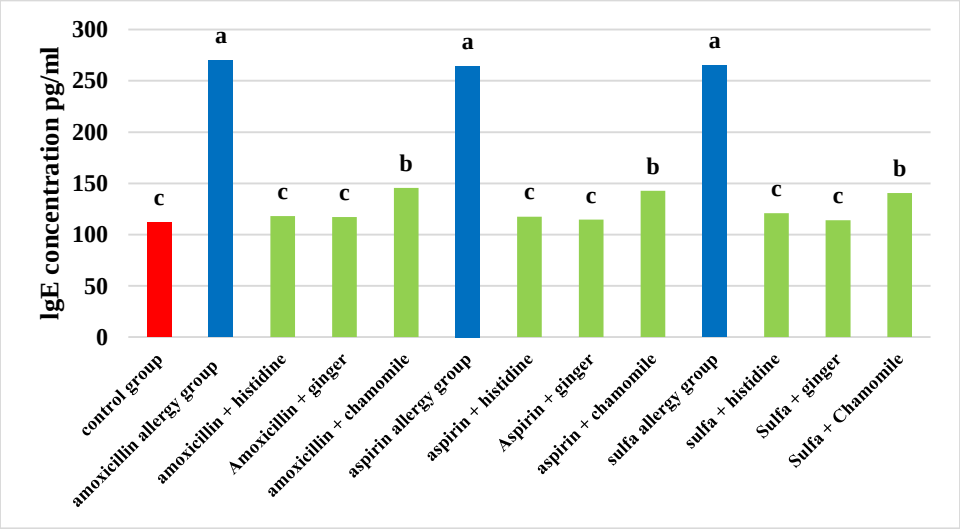


Figure (1) IgE concentration in the studied groups (different letters mean a significant difference at the level of significance ($p<0.05$)).

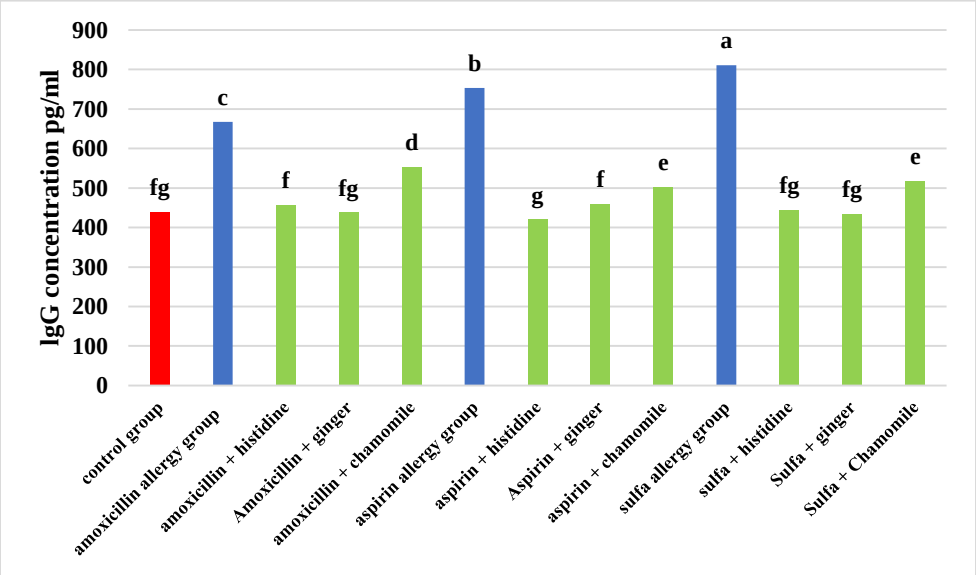


Figure (2) IgG concentration in the studied samples (different letters mean a significant difference at the level of significance ($p<0.05$)).

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The results shown in Figure (2) indicate that there is a significant increase at the probability level ($p<0.05$) in the concentration of IgG 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 IgG 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 the concentration of IgE and IgG in the serum of rats in the groups treated with amoxicillin, aspirin and sulfa in comparison with the healthy control group, the occurrence of allergic reactions in the amoxicillin group can be attributed to the fact that it belongs to the group of beta-lactam antibiotics (BL)), and it is one of the most common drugs that cause allergic reactions because it has small molecular weights that enable it to activate the immune system and the occurrence of an immune response, while by recognizing small molecules by B cells or T cells, and this can be explained by the concept of Hapten, an example of which is penicillin, and Haptens are chemically reactive small molecules that often have a molecular weight of less than 1000 Daltons and are able to undergo a stable covalent bond it form proteins or peptides of higher molecular weight, which leads to an immune response, an immune response can also occur through the so-called pharmacologic, which is the interaction of drugs with immune receptors, and it is called the (p-i) concept, as the drug is inactive in its original form without binding to a carrier molecule or being treated in another way, however, the immune system can be activated by binding directly to immune receptors such as the T-cell receptor (TCR) of specific T cells or specific molecules antigens, when the binding between the drug and proteins is sufficient, this leads to signal transduction through TCRs, which leads to the stimulation of T cells and the occurrence of an immune response that leads to the release of IgE, IgG antibodies, inflammatory cytokines and histamine, and the result agreed with the result of (Chiriac and et al., 2019).

The cause of allergy in the sulfamethoxazole group may also be attributed to the fact that this drug interacts directly with the immune receptors of T-lymphocytes according to the p-i Pharmacologic concept, as the drug is recognized directly by the cells of the immune system, and this result agreed with the findings of (Dorn and et al., 2018).

The mechanism of drug allergy in the aspirin group, according to the interpretation of Szczeklik in 1975, can also be attributed to a group of non-steroidal anti-inflammatory drugs (NSAIDs), as these drugs, including aspirin in particular, act as inhibitors of cyclooxygenase (COX-1) , which leads to a shift in the metabolism of arachidonic acid from cyclooxygenase to the lipid pathway with an increase in the production of Cysteinyl (CysLT) Leukotrienes, which results in a decrease in the amount of PEG2 prostaglandins, as during aspirin reactions the mediators of allergy and inflammation such as (CysLT), eosinophil cationic protein are released (ECP) tryptase, which leads to activation of mast cells and eosinophils, and amplification of other immune cells, which is also a cofactor for drug allergy.

The results also showed a significant decrease in the concentration of IgE and IgG in the serum of rats when treated with histidine, this decrease can be attributed to the fact that this drug belongs to the group of first-generation histamine receptor antagonists, which is an effective drug with anti-allergic properties, Histidine binds to H1 receptors in different cells and causes a decrease in vascular permeability (prevents edema and redness) and reduces smooth muscle tension (bronchiectasis), it

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reduces the activation of peripheral pain receptors (reduces pain and itching), and first-generation antihistamines such as histidine can block the release of histamine from mast cells and basophils and thus reduce Icam-1 expression in epithelial cells, inhibit allergic reactions and regulate the action of cell mediators.

The results also showed a significant decrease in the concentration of IgE and IgG in the blood serum of rats treated with aqueous extract of chamomile and ginger plants, this decrease can be attributed to the role of plant extracts of medicinal importance in inhibiting the toxic effect of some anti-inflammatory drugs and antibiotics through their neutralizing effect. Zingiber officinal is one of the most widely consumed spices in the world, and has a long history of being used as herbal medicine to treat a variety of ailments. It has been used in traditional Thai medicine as well as in Chinese medicine as part of herbal remedies for conditions such as cold, constipation and insomnia and the efficacy of the aqueous and ethanolic extract has been demonstrated as it exhibits the highest anti-allergic activity by inhibiting B-hexosaminidase. Moreover, many experimental and live studies have proven that ginger and its bioactive compounds especially Shogaol-6, gingérol-6 possess strong anti-allergic activity, it suppresses the secretion of immunoglobulins in serum from mast cells and basophils, also, the compounds Shogaol-6, gingérol-6 can inhibit the production and proliferation of cytokines from T cells, and thus B cells as well, thus making it impossible to activate the mast cell, which leads to lowering of immune globulins, this result is consistent with the study of (Yamprasert and et al., 2020), and (Tan and et al., 2018). Matricaria chamomilla, a herb that was known in ancient Egypt and Rome, is one of the most famous medicinal plants used in the world, it contains the main active compounds, bisabolol, bisabololoxide, bisabolonoxide, and chamazulene, and it contains 0.75% of blue color volatile oil Chamomile is known for its anti-inflammatory and anti-allergic activity through the phenolic compounds it contains, as it contains a variety of anti-allergic compounds that can inhibit histamine release by acting directly on the ion-gated mechanism to block the movement of calcium from the extracellular environment into the cytosol, as chamomile flowers are used against allergic diseases and it still occupies a place in traditional oriental medicine, these results agree with the results of (Wu and et al., 2012).

**The concentration of creatinine and albumin in the blood serum:**

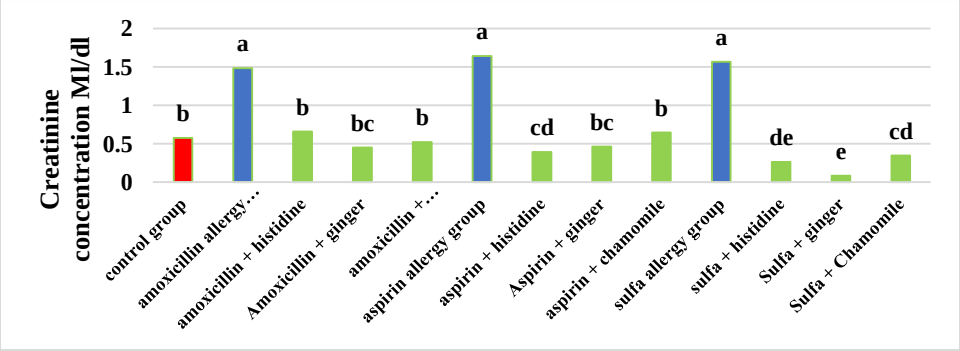


Figure (3) Creatinine concentration in the studied groups (different letters mean there is a significant difference at the level of significance ($p<0.05$)).

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The results shown in Figure (3) indicate a significant increase at the probability level ($p<0.05$) in the creatinine 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 the concentration of creatinine in the blood serum of rats after treatment with aqueous extracts of ginger, chamomile, and histidine group compared to its concentration before treatment.

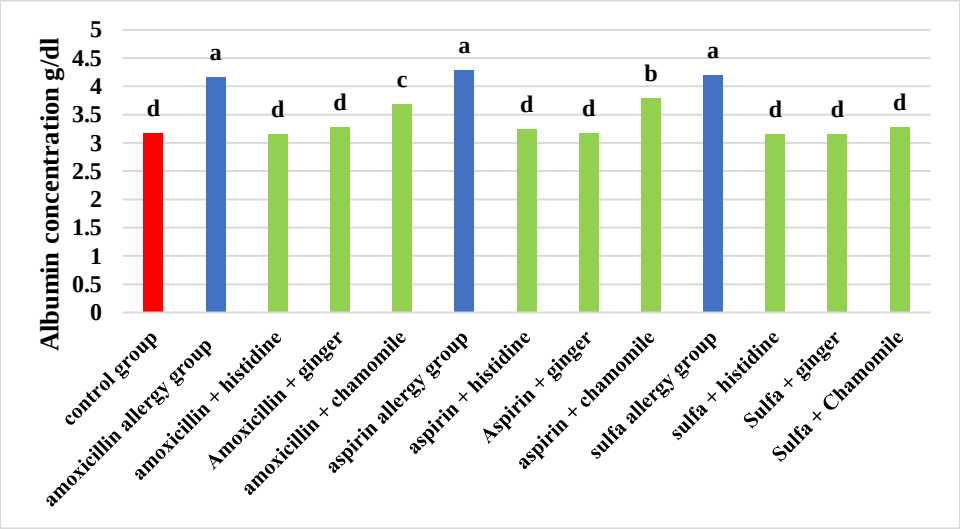


Figure (4) the concentration of Albumin in the studied groups (different letters mean there is a significant difference at the level of significance ($p<0.05$)).

The results shown in Figure (4) indicate a significant increase at the probability level ($p<0.05$) in the albumin concentration 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 albumin concentration 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 creatine in the allergic groups (amoxicillin, aspirin and sulfa group) can be attributed to complications that occur in some organs of the body as a result of oxidative stress that affects the liver, causing malfunctions in the work of the pancreas and loss of insulin and thus cells lose the direct source of energy within cells (glucose), which The animal is forced to use the muscles as an alternative source of energy, which results in the metabolism of large amounts of creatinine, or, the cause of the rise may be the chronic complications that occur in the kidneys, which leads to slow and gradual negative changes in its function, as it causes a functional disorder in the cells of the inner layer of the glomerular capillary vessels, which results in a high concentration of creatinine in the blood and a decrease in its excretion in the urine, this result is consistent with (Yassery, 2018) study.

The results also showed a significant increase in the effectiveness of albumin in the affected groups compared to the healthy control group, and this increase can be attributed to a defect in the filtration functions of the kidneys and an increase in glomerular pressure, thus increasing the rate of albumin

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excretion, research also indicates that the high concentration of albumin is the result of the protective effect of the albumin molecule because it contains the ionic and hydrophobic character, this characteristic of the albumin molecule gives it an antioxidant status, through its association with metallic elements that are positively charged and that participate in the occurrence of oxidation with its various reactions when it is in its free form, because it is prevalent in the blood plasma, which is subject to continuous oxidative stress, so the quantitative effect of the albumin molecule may play its role in being a good antioxidant.

The results also showed a significant decrease in the activity of creatinine and albumin in the histidine group compared to the affected groups (amoxicillin group, aspirin group and sulfa group), this decrease can be attributed to the anti-allergic and anti-inflammatory properties of Histidine, and thus the suppression of inflammatory factors that may have a role in cell hyperplasia and body fluid retention, reducing the inflammation leads to a decrease in the concentration of creatinine in the blood by releasing body fluids and reducing cell hypertrophy, and the anti-inflammatory and antioxidant properties led to a decrease in the effectiveness of albumin in the blood serum.

The results also showed a significant decrease in the activity of both creatinine and albumin in the blood serum of the treated groups, treated with aqueous extracts of ginger and chamomile plants compared to the infected groups, this decrease can be attributed to the anti-inflammatory therapeutic properties found in plant extracts such as phenolic compounds and flavonoids that reduce inflammation and act as an antioxidant and suppress free radicals and reactive oxygen species, which leads to a decrease in the concentration of albumin and creatinine in the blood serum, also, plant extracts, through their anti-inflammatory action, reduce water and electrolyte retention and reduce cell tension and swelling, which leads to a reduction in albumin and creatine concentrations in the blood serum by eliminating creatine through urine because it is a droppings product.

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