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The effect of silver nanoparticles of aqueous *Matricaria chamomilla* extract on acute liver toxicity caused by acetaminophen in mice

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Abstract

Attention to the daily prescription of large amounts of drugs by doctors; In recent years, much attention has been paid to the effect of plants in the treatment and prevention of drug poisoning. *Matricaria chamomilla* is one of the oldest medicinal plants known to man and its use dates back to ancient Greece. In this research, the protective effect of green tea extract in hepatotoxicity caused by acetaminophen has been investigated. So that 48 adult male mice were randomly divided into 6 groups. The control group received only physiological serum. *M. chamomile* group received 250 mg/kg and (AgNP) *M chamomilla* received 0.5 mg/kg for 30 days; The acetaminophen group was prescribed 500 mg/kg of acetaminophen orally, and the experimental groups (acetaminophen + *M. chamomile* extract) were given chamomile extract with a dose of 250 mg/kg and (silver nanoparticle of *M. chamomile* plant + acetaminophen) (AgNP) *M chamomilla* with a dose of 0.5 received mg/kg for 30 days and a toxic dose of acetaminophen was prescribed on the 29th day. On the 31st day, blood was drawn to measure alanine transferase (ALT) and aspartate transferase (AST), and after that, the animals' livers were placed in 10% formalin for histopathological examination. The serum levels of ALT and AST enzymes in the silver nanoparticle group were significantly reduced compared to other groups. ($P<0.05$) so that in histopathological studies, liver necrosis, congestion of red blood cells and the accumulation of inflammatory cells in (AgNP) *M. chamomilla* were reduced compared to the acetaminophen group. According to the results of this research (AgNP) *M chamomilla* is probably involved in liver necrosis caused by acetaminophen. It has a protective role.

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Introduction

Acetaminophen is a common analgesic and antipyretic drug, which in high doses leads to liver and kidney necrosis in humans and animals [1-2]. In the past, the use of acetaminophen has increased greatlyMany doctors have sufficient information about the symptoms of poisoning with this drug and the details of its treatment. [3-4] Since liver damage caused by acetaminophen can lead to death, finding a combination that can neutralize its effect seems necessary. The use of medicinal plants for the treatment of diseases has been common in human societies for a long time, and until about half a century ago, plants were considered one of the most important sources of providing medicine for the treatment of pain. The necessity of fundamental and real investigation of traditional medicine and medicinal plants has been felt for a long time in the scientific societies of our country, and in recent years much attention has been paid to the necessity of investigating medicinal plants [5-6] . During the last decade, a large number of plant products and food compounds have been investigated as liver protectors. Ayman and colleagues (2003) showed that the administration of Arabic gum reduces hepatic necrosis and the acute increase of serum aminases caused by acetaminophen in a way that the protective effect of St. [7] By creating toxic compounds, free radicals can lead to adverse effects such as inflammatory diseases, diabetes, heart and brain ischemia, cancer, immune deficiency, and aging in the human body. become Therefore, it seems necessary to use antioxidants to slow down the rate of oxidation. Recently, after realizing the toxicity and carcinogenicity of many synthetic antioxidants, the attention of researchers has been directed to the identification of antioxidants taken from natural sources. In a study, the antioxidant activity of chamomile essential oil was investigated by the alpha-carotene test method, and the results of this study show that chamomile essential oil can show the greatest inhibitory effect on free radicals (82.5 percent) after 120 minutes [8]. In another study, the antioxidant capacity of alcoholic chamomile extract was measured by copper ion reduction method, and informed results showed that chamomile extract has strong antioxidant properties. Chamomile also has the property of regenerating iron ions, which proves its strong antioxidant effects [9]. The main properties of silver nanoparticles are: not causing sensitivity, high stability, being hydrophilic, compatible with the environment, resistant to heat, not creating or increasing resistance and compatibility in microorganisms. Also, they have great ability to be added to fibers, polymers, ceramics, stones, and colors without changing the properties of the material. The antibacterial property of silver nanoparticles has led to the expansion of its applications in the fields of textiles, paint industries, ceramics, pharmaceuticals, agriculture, animal husbandry, food packaging, and cosmetic-sanitary supplies [10].

Materials and methods

Plant collection

Matricaria chamomilla were collected from Kermanshah province and sent to the herbarium of Kermanshah Agricultural Jihad Research Center to identify and confirm the genus, species and subspecies.

Plant extraction

In order to prepare alcoholic extract, after completely drying the plant in a dark place without humidity for a week, the young leaves of the plant were separated from other parts and then crushed completely. 150 grams of plant powder was carefully weighed and 450 milliliters of absolute ethanol was poured on it (1/3 weight/volume ratio), the mixture was heated for 2 hours at 40 degrees Celsius and stirred at the same time. Then for 24 hours at room temperature the medium was placed, and after that, the extract was filtered by Whatman No. 2 paper (Whatman, UK). The primary extract entered the machine. Vacuum distillation (rotary with vacuum pump, Heidolph and Collegiate, LABOROTA 4000, Germany) at a temperature of 80 degrees Celsius and for one hour, the solvent was evaporated and the concentrated extract was obtained.

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Preparation and synthesis of

AuNPs@MC For each synthesis, *G. tournefortii* extract once separately and another time together (10 mL) was added to aqueous solution of (1 mM) HAuCl4×H2O (100 mL) at room temperature and stirred, color of the solution turned to dark red, that indicated formation of gold nanoparticles. The solution stirred for 1 h to complete reduction process, then centrifuge at 12,000 rpm for 15 min and upper phase was removed, obtained AuNPs was washed several times with deionized water to remove all uncoordinated biological materials, then put it in the oven at 50 °C to dried

Animals

In this study, 48 adult and healthy Wistar male mice weighing 3±36 grams were purchased from the Laboratory Animal Breeding Center of Urmia University of Medical Sciences Faculty of Pharmacy and kept at a temperature range of 2±2°C and 12 hours of light and 12 hours of darkness. Animals have unlimited access to food and water.

Experimental design

The animals were randomly divided into 6 groups: Control group: Animals received physiological serum for 30 days. Acetaminophen group: The rats in this group received 250 mg/kg of acetaminophen orally and by gavage. Group 3: The animals of this group were treated with *Matricaria chamomilla* extract at the rate of 500 mg/kg for 30 days. Group 4: The animals of this group were treated with AuNPs@MC at the rate of 0.5 mg/kg for 30 days. Group 5 (*M. chamomile* extract + acetaminophen): Chamomile extract was given at the rate of 250 mg/kg for 30 days, and in addition, a toxic dose (500 mg/kg) of acetaminophen was given on the 29th day. It was prescribed. Group 6 (AuNPs@MC + acetaminophen): AuNPs@MC was given at the rate of 0.5 mg/kg for 30 days, and in addition, on the 29th day, a toxic dose (500 mg/kg) of acetaminophen was also prescribed. became. Therefore, on the 31st day after anesthesia, blood was drawn from the jugular veins of the animal's neck to measure serum transaminases (ALT) and AST. Serum aminases were measured manually using the Sigma kit.

Histological study

After blood collection, mice were sacrificed by cervical vertebrae displacement method and their livers were isolated and for histopathological studies, they were fixed in 10% formalin. After 48 hours, tissue preparation was done and paraffin blocks were prepared and 5-micron thick paraffin sections were taken using a rotary microtome. Then, the slices were stained with hematoxylin and eosin staining method and were studied by light microscope.

Statistical Methods

In the case of quantitative data, two-way ANOVA was used, followed by Tukey's method. All the results were expressed as (M±SD) and the significance level of the results was considered at least $P<0.05$.

Results

Histopathological studies Histopathological studies showed that in the control group and the group of *M. chamomile* extract and especially AgNPs@MC, which had received physiological serum and 250 mg/kg and 0.5 mg/kg orally for 30 days, respectively The liver tissue was normal and no evidence of liver necrosis was observed. In the poisoned group that received only acetaminophen, necrosis of the center of the lobules, aggregation of inflammatory cells and congestion.Severity was observed throughout the studied slides, which was evident in the form of the disappearance of the cytoplasmic borders of the liver cells in the necrotic areas and changes in the nucleus of the cells (slippage, fragmentation and crumpling of the nucleus) (Fig.1) In the experimental group that had received AgNPs@MC, 30 Day compared to the group that had received *M. Chamomile*. The extent of necrosis was not reduced. So that there was a large number of healthy lobules, and in the involved lobules, in addition to a noticeable

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reduction in the area of necrosis, the accumulation of inflammatory cells and congestion was less than in the poisoned (acetaminophen) group (Figure 2).

Biochemical studies

Biochemical results obtained from the measurement of enzymes Serum ALT and AST are shown in Table 1. So that in the acetaminophen group, the level of ALT and AST in the serum showed an acute increase, which is indicative of liver necrosis, and it has a statistically significant difference from the control group. While there was no significant difference between AgNPs@MC and the control group. Therefore, the difference between the experimental group and the poisoned group was significant ($P<0.01$) and there was also a significant difference between the experimental group and the control group.

Discussion

Acetaminophen is converted by the cytochrome P450 system into a toxic metabolite called N-acetylparabenzoquineimine (NAPQI), this metabolite is converted to water-soluble mercapturic acid by connecting with glutathione and excreted through the kidneys. An excess of toxic metabolites causes depletion of available glutathione and causes necrosis. In the group that received (poisoned) acetaminophen, liver necrosis was observed mostly in the center of the lobule, where there are more amounts of cytochrome P450[29]. The results obtained from the present study show that the administration of AgNPs@MC significantly reduces the severe increase in serum transaminases caused by the results of the histopathological studies are also consistent with the above findings and the experimental group can be reduced in comparison with the poisoned group. It showed observations in necrosis and liver damage. Examining the results of liver biochemical tests showed that liver transaminases increased in the test group compared to the control group and the *M. chamomile* extract group. This means that although the consumption of AgNPs@MC for one month in the amount of 0.5 mg/kg reduces the liver damage caused by acetaminophen, it does not completely prevent liver damage. The effect of hydroalcoholic extract of chamomile flower on the proliferation and apoptosis of neural stem cells in the condition of oxidative damage has been investigated. In a study, neural stem cells were extracted from the hippocampus region of the brain of a desert mouse baby. The cells were treated for 48 hours with the concentrations of 200, 400, 600, 800 and 1000 micrograms per milliliter of culture medium and the cell proliferation rate was checked by MTT method. The results of this study showed that the proliferation of neural stem cells in the presence of the hydroalcoholic extract of the chamomile plant increases significantly compared to the control group and the percentage of apoptotic cells decreases. Progenitor cells derived from adult rat hippocampal neurons as well as hippocampal stem cells were investigated. By stimulating the differentiation of neurons, apigenin increased and accelerated neurogenesis in in vitro and in vivo environments. Apigenin also improved the memory and learning of rats in the Morris water maze test [11].

conclusion

According to the results of the present study, which confirm the protective and healing effects of plant AgNPs@MC on liver toxicity, it seems that low and medium doses of this plant, due to its antioxidant and anti-inflammatory compounds, can prevent the destruction of liver tissue and increase the antioxidant system by strengthening the antioxidant system. Prevent liver enzymes caused by it

Authors' contribution

All authors contributed equally to the manuscript.

Conflicts of interest

The authors declared no competing interests.

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Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication and etc.) have been completely observed by author.

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