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ANTIHYPERURICEMIC EFFECT OF ALCOHOLIC GINGER RHIZOME EXTRACT ON POTASSIUM OXONATE, INDUCED HYPERURICEMIC RATS

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Abstract

Current evidences reported that hyperuricemia is closely related to overproduction or under excretion of uric acid (UA). Ginger (*Zingiber officinale*) rhizome has shown therapeutic role in the health management and considered as potential chemo protective agent. In this study we aimed to investigate the ability of ginger rhizome extract to decrease serum uric acid level, xanthine oxidase (XO) enzyme activity and study the oxidative – antioxidant status in hyperuricemic rats induced by intraperitoneal injection of potassium oxonate (PO). The experiment was performed by two parts: First part involved extraction of ginger rhizome by using 70% ethanol solvent and study the phytochemical analysis of ginger rhizome ethanolic extract to determine its components, while the second part involved study the antihyperuricemic effect of alcoholic extract of ginger rhizome on potassium oxonate- induced hyperuricemic rats. In this part of the experiment (48) Swiss albino male rats about three months of age with body weights ranged between 200 – 230 gram were used which were divided randomly into four equal groups, 12 rats in each group and eight subgroups, 6 rats each which were used as follows: Group 1: (negative control) was administered distilled water orally daily for 14 and 28 days. Group 2: (hyperuricemic positive control) was administered potassium oxonate (250 mg/ kg) intraperitoneally once daily for 7 days, then given distilled water orally for 14 and 28 days. Group 3: was administered potassium oxonate (250 mg/kg) intraperitoneally once daily for 7 days, then given ethanolic extract of ginger rhizome (250 mg/kg) orally once daily for 14 and 28 days, while the group 4: was administered potassium oxonate (250 mg/kg) intraperitoneally once daily for 7 days, then given standard drug allopurinol (5 mg/kg) orally once daily for 14 and 28 days. Animals of each group were sacrificed at the end of 14 and 28 days and blood was collected and sera were separated for biochemical analysis and oxidative- antioxidant status tests. The results showed the presence of alkaloids, phenols, flavonoids, tannins, saponins, terpenoids and glycosides as phytochemical components in ginger rhizome ethanolic extract. The results also showed the significant ($P<0.05$) increase in the levels of serum uric acid, xanthine oxidase activity in hyperuricemic positive control group as compared to negative control which accompanied by increasing of serum oxidative malondialdehyde (MDA) enzyme levels while these parameters decreased significantly ($P<0.05$) or reversed in the ginger ethanolic extract group after 14 & 28 days of treatment which accompanied by increasing significantly ($P<0.05$) in the levels of serum antioxidant reduced glutathione (GSH) enzyme as compared to positive control. On the bases of these results, it can be concluded that the administration of the ethanolic extract of Zingiber officinale rhizome at a dose level of (250 mg/ kg) has been exhibited more activity as antioxidant in treating and reduce the harmful effect of hyperuricemia induced by potassium oxonate in hyperuricemic rats.

Key words : Hyperuricemia, Ginger, Rats, Potassium oxonate.

Introduction

Hyperuricemia is a risk factor for diabetes, cardiovascular complications, metabolic syndrome and chronic kidney disease (Jin *et al.,* 2012 and Liu *et al.,* 2015). It is well defined as the overproduction and underexcretion of uric acid in the patients (Chen *et al.,* 2019). During the formation of uric acid xanthine oxidase (XO) is the key enzyme involved in the transformation of xanthine and hypoxanthine into uric acid (Maiuolo *et al.,* 2016). The excessive consumption of purine foods and the lack of genetic enzymes can lead to uricemia and hyperuricemia. The treatment of mild form of

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hyperuricemia is only through dietary restriction of purine rich foods while the moderate to severe forms are treated with pharmacological agents such as allopurinol which is commonly used drug in patients with hyperuricemia who are not responsive to dietary treatment (Stamp *et al.,* 20l6). In uric acid excretion the kidney and the intestine play an important role which that more than 70% of uric acid excretion through the kidney (Lipkowitz, 2012). However, underexcretion of uric acid in the kidney can lead to kidney injury and affect its functions which worsen the renal dysfunction for uric acid excretion (Chen *et al.,* 2019). It is notable that the using of many medications for hyperuricemia have side effects such as hepatitis, nephropathy, and allergic reactions (Burns and Wortmann, 2011), therefore the need for less toxic alternatives is an important (Roddy and choi, 2014). A potential source of such compounds can be obtained from medicinal plants which have the antihyperuricemic effects. *Zingiber officinale* Roscoe (Ginger) is an indispensable component of curry belongs to the Zingiberaceae family which has been used to treat disease including headache, cold, arthritis, renal function and reduces serum creatinine, urea and blood urea nitrogen (Aniess, 2016). The mechanisms of these Reno protective effects may involve both oxidative stress reduction and significant 6- gingerol antioxidant effects (Mahmoud *et al.,* 2012). The major active ingredients in ginger are bisapolene, zingiberene, and zingiberol which have the pharmacological effects such as analgesics, sedative, antipyretic, and antibacterial effects in vitro and in animals (Mascolo and Jain, 1989).

Materials and Methods

Animals

This study was performed under the guidelines supervision of Ethical Committee for lab. Animals work in the College of Veterinary Medicine, University of Baghdad. Forty-eight Swiss albino male rats about three months of age with body weight ranged between 200-230 gm were used to perform the experiment of the present study. Rats were housed in plastic cages of 20×50 ×75 cm dimensions, placed in a special housing room belongs to the Department of Physiology, Biochemistry and Pharmacology/ College of Veterinary Medicine/ University of Baghdad for two weeks for acclimatization. Standard rodent diet (Commercial feed pellets) and tap water were freely available. Housing condition were maintained at 20-25 ^{o}C in air-conditioned room, the air of the room was changed continuously by using ventilation vacuum, while the light/ dark cycle was 12/12 h. in housing place.

Plant Materials

Freshly samples of *Zingiber officinale rhizome* were purchased from Iraqi local market in Baghdad. The samples were oven- dried for 96 h. at 40 ^{o}C. Dried plant materials were grounded by using an electrical blender to fine powder which stored in a dry place in the dark for the experimental study (Al- Azzawie and Abd, 2015).

Extraction of *Zingiber Officinale* Rhizome

The rhizome fine powder of 100 grams was homogenized in 500 ml of 70% ethanol and left in a conical flask at room temperature for 3 days. Then, the mixture was filtered through a fine muslin cloth and a filter paper (What man No. 1). The filtered solution was transferred in hygienic and germ - free petri dish and evaporated at 40 ^{o}C in an incubator for 3 days. The final concentrated extract was then lyophilized and yielded ethanolic extract of rhizomes of Zingiber officinale (Bardi *et al.,* 2013).

Detection of Phytochemical Components of Ethanolic Extract of *Zingiber officinale* Rhizome

1. Detection of Alkaloids: This test was conducted according to (Odebiyi and Sofowora, 1978).
2. Detection of phenolic components: This test was conducted according to (Harborne, 1973).
3. Detection of Flavonoid components: This test was accomplished according to (Jaffer *et al.,* 1983).
4. Detection of Tanins: This test was accomplished according to (Harborne, 1984).
5. Detection of Saponins: This test was done according to (Harborne, 1984).
6. Detection of Steroid and Terpenoid components: This test was performed according to (Al – Bid, 1985).
7. Detection of Glycosides: This test was done according to (Harborne, 1984).
8. Detection of Coumarins: This test was performed according to (Geissmane, 1962).

Preparation the Concentration of *Zingiber officinale* Ethanolic Extract

Stock solution was prepared by mixing 5 grams from dried extract with distilled water and completed the volume to 10 ml to get a concentration of 500 mg/ ml, then the extract was given to rats orally at a dose of 250 mg/ kg according to (Al- Azzawie and Abd, 2015).

Preparation of Potassium Oxonate Solution

Potassium oxonate powder was used. The solution was prepared by taking 2.5 grams of potassium oxonate powder and completed to 10 ml of normal saline to get a concentration of 250 mg/ml which was given to rats

intraperitoneally at a dose of 250 mg/kg according to (Hall *et al.,* 1990).

Preparation of Allopurinol Solution

Allopurinol 300 mg tablet was used. The stock solution was prepared by dissolving 300 mg tablet in 10 ml of distilled water to get a concentration of 30 mg/ml, then was given to rats orally once daily at a dose of 5 mg/kg according to (Al- Azzawie and Abd, 2015).

Experimental Design

Total of 48 male rats were divided randomly into four equal groups, 12 rats in each group. Treatments began with schedule as follows:

G(1): Negative control was administered distilled water orally for 14 and 28 days.

G(2): Hyperuricemic positive control was administered potassium oxonate 250 mg/kg intraperitoneally for 7 days, then given distilled water orally for 14 and 28 days.

G (3): Was administered potassium oxonate 250 mg/ kg intraperitoneally for 7 days, then given ethanolic extract of ginger rhizome 250 mg/ kg orally for 14 and 28 days.

G (4): Was administered potassium oxonate 250 mg/ kg intraperitoneally for 7 days, then given standard drug allopurinol 5 mg/ kg orally for 14 and 28 days.

Parameters Studied

After the end of 14 and 28 days of treatments of each group, the rats blood samples were collected via the heart puncture. Blood was kept in gel tubes and serum was isolated after centrifugation at a speed of 3000 (rpm) for 15 minutes, which were stored at (- 20 ^{o}C) until analysis for:

1. Biochemical tests:
   - Serum uric acid levels
   - Serum xanthine oxidase activity
2. Parameters related to oxidant - antioxidant status:
   - Serum reduced glutathione (GSH) concentration.
   - Serum malondialdehyde (MDA) concentration.

Statistical Analysis

The statistical analysis of the data of the experiment was measured by using the IBM SPSS Statistical (version 26.0), Using of one-way ANOVA and Least significant differences (LSD) post hoc test were performed to assess significant differences among means of the groups. The results were expressed as mean ± stander errors and $P < 0.05$ was considered statistically significant (IBM Corp, 2019).

Results

The percentage of extract that obtained was 30.5%. The phytochemical analysis of ginger rhizome ethanolic extract revealed the presence of Alkaloids, Phenols, Flavonoids, Tannins, Saponins, Terpenoids and Glycosides as shown in table 1.

The levels of serum uric acid and xanthine oxidase (XO) activity are represented in tables 2 and 3 which showed significant ($P<0.05$) increase in their values in serum of rats in (G2) hyperuricemic positive control group that received pot. oxonate at the period of 14 and 28 days of treatments as compared to (G1) negative control group, while there were significant ($P<0.05$) decrease in the values of serum uric acid and xanthine oxidase activity in the hyperuricemic groups (G3 and G4) that received ethanolic extract of ginger rhizome and allopurinol respectively as compared to (G2) hyperuricemic positive control group.

Table 1: Phytochemical analysis of ginger rhizome ethanolic extract.

No	Phytochemical constituents	Identification
1	Alkaloids	+
2	Phenol	+
3	Flavonoids	+
4	Tannins	+
5	Saponins	+
6	Steroids	-
7	Terpenoids	+
8	Glycosides	+
9	Coumarins	-

(+) indicates presence of the phytochemical constituents.

Table 4 shows the levels of serum reduced glutathione (GSH) of all groups. The results show there were significant ($P<0.05$) decrease in GSH levels in serum of rats in (G2) hyperuricemic positive control group at the periods of 14 and 28 days of treatments as compared to (G1) negative control group, while there were significant ($P<0.05$) increase in GSH levels in (G3 and G4) hyperuricemic groups that received ethanolic extract of ginger rhizome and allopurinol respectively in comparison with (G2) hyperuricemic positive control group, while the levels of serum malondialdehyde (MDA) show significant ($P<0.05$) increase in the (G2) group in the periods of 14 and 28 days of treatments as compared to (G1) group that received distilled water and there were significant ($P<0.05$) decrease in the values of (MDA) in serum rats of (G3 and G4) groups as compared to (G2) group, (Table 5).

Discussion

In this study the administration of potassium oxonate (PO) for 7 days followed by ginger rhizome ethanolic extract for period of 14 and 28 days showed anti –

Table 2: The effects of *Zingiber officinale* rhizome ethanolic extract on serum uric acid in hyperuricemic rats (mg/ dl).

Groups	Mean ± SE	
	14 Days	28 Days
G (1): Negative control Distilled water orally	1.27 ± 0.15 B	1.24 ± 0.18 B
G (2): Hyperuricemic positive control Pot. Oxonate I/P (250 mg/kg) for 7 days	4.47 ± 0.18 A	4.65 ± 0.36 A
G (3): Pot. Oxonate I/P (250 mg/kg) for 7 days then ginger rhizome ethanolic extract (250 mg/kg) orally	1.52 ± 0.18 B	1.48 ± 0.26 B
G (4): Pot. Oxonate I/P (250 mg/kg) for 7 days then allopurinol (5 mg/kg) orally	1.33 ± 0.14 B	1.29 ± 0.24 B

Values are presented as mean ± SE.

Capital different letters denoted to ($P<0.05$) significant differences between groups.

Table 3: The effects of *Zingiber officinale* rhizome ethanolic extract on serum xanthine oxidase (XO) in hyperuricemic rats (U/ L).

Groups	Mean ± SE	
	14 Days	28 Days
G (1): Negative control Distilled water orally	0.32 ± 0.07 B	0.35 ± 0.04 B
G (2): Hyperuricemic positive control Pot. Oxonate I/P (250 mg/kg) for 7 days	0.80 ± 0.03 A	0.78 ± 0.03 A
G (3): Pot. Oxonate I/P (250 mg/kg) for 7 days then ginger rhizome ethanolic extract (250 mg/kg) orally	0.41 ± 0.02 B	0.40 ± 0.03 B
G (4): Pot. Oxonate I/P (250 mg/kg) for 7 days then allopurinol (5 mg/kg) orally	0.37 ± 0.05 B	0.35 ± 0.04 B

Values are presented as mean ± SE.

Capital different letters denoted to ($P<0.05$) significant differences between groups.

Table 4: The effects of *Zingiber officinale* rhizome ethanolic extract on serum reduced glutathione (GSH) in hyperuricemic rats (µmol/L).

Groups	Mean ± SE	
	14 Days	28 Days
G (1): Negative control Distilled water orally	4.68 ± 0.28 B	4.87 ± 0.24 B
G (2): Hyperuricemic positive control Pot. Oxonate I/P (250 mg/kg) for 7 days	1.50 ± 0.15 C	1.55 ± 0.14 C
G (3): Pot. Oxonate I/P (250 mg/kg) for 7 days then ginger rhizome ethanolic extract (250 mg/kg) orally	4.93 ± 0.19 AB	5.10 ± 0.17 AB
G (4): Pot. Oxonate I/P (250 mg/kg) for 7 days then allopurinol (5 mg/kg) orally	5.43 ± 0.21 A	5.50 ± 0.25 A

hyperuricemic effect that reflected by reducing the elevation in serum uric acid levels and xanthine oxidase (XO) activity which accompanied by decreasing the serum levels of oxidative stress enzyme malondialdehyde (MDA) and increasing the levels of serum antioxidant reduced glutathione enzyme (GSH). A number of studies indicated that ginger exhibits antioxidant activity and anti-free radicals abilities that stimulate urea synthesis (Polasa and Nirmala, 2003). Xanthine oxidase (XO) is the enzyme involved in conversion of xanthine and hypoxanthine to uric acid (Si *et al.,* 2018). The higher XO activity can lead to excessive synthesis of uric acid (Zhao *et al.,* 2006). Treatment with ginger ethanolic extract could significantly inhibit XO activity in serum suggesting that effect on decreasing uric acid might be due to inhibitory effect on XO level. The recent findings after 14 and 28 days showed that ginger rhizome ethanolic extract can decrease uric acid level might be attributed to the presence of active compounds in ginger rhizome such as glycine, ascorbic acid and fiber that have uricosuric effect and hypouricemia (Aniess, 2016). Flavonoids from ginger rhizome and most plants are one of the groups of phytochemicals that provide antioxidants properties of most plants which showed significant inhibition of xanthine oxidase (Hilario *et al.,* 2017). In this study the ethanolic extract of ginger rhizome was shown to have a hypouricemic effect comparable with allopurinol which could be used as a potential alternative in the treatment of hyperuricemia. The mechanism of action of allopurinol is the inhibition of XO enzyme, also purified bioactive compounds from

Table 5: The effects of *Zingiber officinale* rhizome ethanolic extract on serum malondialdehyde (MDA)) in hyperuricemic rats (µmol/L).

Groups	Mean ± SE	
	14 Days	28 Days
G (1): Negative control Distilled water orally	4.01 ± 0.36 B	4.18 ± 0.25 BC
G (2): Hyperuricemic positive control Pot. Oxonate I/P (250 mg/kg) for 7 days	9.06 ± 0.27 A	9.10 ± 0.23 A
G (3): Pot. Oxonate I/P (250 mg/kg) for 7 days then ginger rhizome ethanolic extract (250 mg/kg) orally	4.43 ± 0.24 B	4.38 ± 0.22 B
G (4): Pot. Oxonate I/P (250 mg/kg) for 7 days then allopurinol (5 mg/kg) orally	3.68 ± 0.32 B	3.62 ± 0.31 C

Values are presented as mean ± SE.

Capital different letters denoted to ($P<0.05$) significant differences between groups.

plants that have hypouricemic property showed competitive inhibition of XO enzyme in both in vitro and in vivo studies (Wang *et al.,* 2004). Most of these natural products report that the uric acid lowering property is secondary to the antioxidant property of these products (Ma *et al.,* 2014& Kostic *et al.,* 2015). Ginger significantly reduces serum uric acid and XO enzyme activity, the mechanisms of these protective effects may be outcomes of 6- gingerol which act as antioxidant effect as recorded by (Mahmoud *et al.,* 2012).

The lowest XO enzyme activity of ginger extract is due to the fact that secondary metabolites in ginger contain diverse classes of bioactive phenolic compounds such as polyphenols and alkaloids which may act as XO inhibitor beside that ginger major active ingredients such as gingerone, gingerdiol, zingibrene, gingerols and shagaols are known to possess antioxidant activities which maintain the liver normal functions by accelerating the regenerative capacity of its cells (Ajeel and Al- Faragi, 2013).

Conclusions

From the data of our study, we could conclud that the Zingiber officinale rhizome ethanolic extract has hypouricemic effect in hyperuricemic rats – induced by potassium oxonate due to decrease the excessive increasing of serum uric acid by decreasing the activity of serum xanthine oxidase enzyme and by its acting as antioxidant agent. Our findings also suggest that ginger ethanolic extract could be used as a new potential drug in protecting against hyperuricemia which cause harmful effects.

Recommendations

We suggest that ginger ethanolic extract could be used in the research and development of hypouricemic drugs of natural products which are inexpensive with high safety profile.

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