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Effect of orally administered aqueous extracts of selected Jordanian plants and paracetamol on routine clinical chemistry tests in human volunteers

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Abstract

Medicinal herbs are commonly used by people in Jordan. In the current study, we attempt to see whether the oral administration of aqueous extracts and paracetamol on human volunteers for 5 days affect the results of clinical chemistry tests of serum. A total of 54 healthy volunteers were divided into six groups of nine, with the first five groups drinking 200-250 ml of aqueous extract from selected medicinal plants for five days and the sixth group taking two 500 mg paracetamol tablets for five days. Blood samples were obtained before to set as the control group without any treatment and one hour after the first dose of administration in day 1, as well as one day after the fifth dose in day 5. The serum was subjected to 13 conventional clinical chemistry assays. Oral administration of aqueous extracts of *R. officinalis*, *V.triphylla*, *Z.officinale*, *S.triloba* and *O.syriacum* for 5 days cause a significant increase or decrease of some clinical chemistry tests (BUN, CREA and LDH; clinical parameters were decreased) compared to 0 time of administration. The potential risks of *O. syriacum*, increased ALP, *S. triloba* increased K and *V. triphylla* increased uric acid. Although, some clinical chemical tests were affected by these aqueous extracts, but these effects did not exceed the known normal ranges of these parameters, therefore it is concluded that the oral administration of aqueous extracts of tested herbs could significantly alter some laboratory results without exceed the normal range of results.

1. Introduction

Medicinal herbs play an important role in folk medicine in Jordan (Abdelhalim *et al.*, 2017; Issa and Basheti, 2016; Issa and Basheti, 2017; Abu-Irmaileh and Afifi, 2003).

Rosmarinus. officinalis L. (Lamiaceae), the Arabic name is Ikleel al-Jabaland, English name is rosemary; it has been widely used in cooking to change and improve flavors, it is used to prevent and cure colds, rheumatism, pain of muscles and joints in folk medicine. rosmary extracts have a variety of pharmacological activities, such as antiinflammatory, antimicrobial, antioxidant, antidiabetic and antitumor activities (Faixová and Faix, 2008; Andrade *et al.*, 2018; Rocha *et al.*, 2015; Eilyad *et al.*, 2012).

Zingiber officinale Roscoe belongs to the family of Zingiberaceae, ginger is the common name for *Zingiber officinale* Roscoe. Ginger extract has been examined for its pharmacological and biological effects, such as antioxidant, antiinflammatory, antimicrobial, antiobesity, antidiabetic, antinausea and antiemetic, cardiovascular protection, neuroprotection and antiallergen (Sharifi-Rad *et al.*, 2017; Mao *et al.*, 2019).

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Salvia triloba, L., belongs to the Lamiaceae family, commonly referred to as Greek sage, the Arabic name is Meramiyyh is a native plant of the Mediterranean, which has been used in traditional medicine to treat gastric disorders, bloating, infections of the mouth, gums, and teeth, stomach discomfort, headaches, common cold, cough, and influenza (Abu-Irmaileh and Afifi, 2003; Abu-Rmailah and Afifi, 2000; Hala, 2006). *S. triloba* extracts have been shown to possess antioxidant, antiinflammatory, anticancer and antimicrobial activities (Kamatou *et al.*, 2010; Kamatou *et al.*, 2008; Kamatou *et al.*, 2007; Kamatou *et al.*, 2005; Hala, 2006).

Origanum syriacum L. (Lamiaceae), is often known as white oregano and/or Syrian oregano, and its Arabic name is za'atar (Zein *et al.*, 2011). Previous studies have reported its antioxidant, anti-inflammatory and anticholinesterase activities (Loizzo *et al.*, 2009).

Verbena triphylla, L'Her, belongs to the Lamiaceae family, English name is lemon verbena, the arabic name is melissa. It is commonly used to treat abdominal pain, gynecological disorders, arthritis (Abu-Irmaileh and Afifi, 2003; Abu-Rmailah and Afifi, 2000).

Paracetamol is a non-prescription analgesic and antipyretic medication that is available in mono- and multi-component formulations around the world.

The purpose of this study is to examine if oral administration of aqueous extracts of *Z.officinale* (rhizomes), *R. officinalis* (leaves), *V. triphylla* (leaves), *S.trialob* (leaves), *O.syriacum* (leaves) on human volunteers for 5 days affect the results of clinical chemistry tests of serum against the well-known drug paracetamol.

2. Materials and Methods

2.1 Plant material

The selected plants Ginger (rhizomes), Rosemary (leaves), Melissa (leaves), Meramiyyh (leaves), Za'atar (leaves) were obtained at Madaba, Jordan's local herbal stores.

i. Preparation of aqueous extracts

250 g of Ginger, Rosemary, Melissa, Meramiyyh and Za'atar were boiling at 100°C for 10-15 min and then soak for 4-5 h at 25°C. The soaking or aqueous extract was then put into clean bottles (each one contains 1.250 l).

ii. Samples of blood

Table 1 shows the demographic characteristics of 54 healthy volunteers who were divided into six groups of nine. For five days, five groups drank 200-250 ml of aqueous extracts of Ginger, Rosemary, Melissa, Meramiyyh, and Za'atar daily, while group six was given two 500 mg paracetamol pills. In gell tubes, three (03) blood samples were taken from each healthy volunteer (before consuming aqueous extract (0 time), after 1 h of the first dose (drinking aqueous extract) on day 1, and the next day following the last dose of day 5, day 6). To separate and collect serum, gell tubes were centrifuged for 10 min at 3000 xg at 25°C. The supernatant was collected after 2ml of distilled water was introduced to the cells under the gell in tubes, and the tubes were centrifuged for 5 min at 3000 xg (hemolysate). Until analysis, all samples were maintained frozen at – 20°C.

Table 1: Demographic data of participant

Group	Age (Mean ± S.D.)	Female/Male
Origanum syriacum	35.8 ± 14.7	4/5
Salvia triloba	42.8 ± 14.6	6/3
Verbena triphylla	34 ± 18.6	4/5
Zingiber officinale	41.8 ± 7.6	7/2
Paracetamol	30.6 ± 9.8	3/6
Rosmarinus officinalis	35.4 ± 13.5	4/5

iii. Measurement of clinical chemistry parameters

The kits for measuring clinical chemistry parameters were purchased commercially from Roche, and the parameters were measured using a Hitachi 902 analyzer. Table 2 shown theclinical chemistry parameters measured.

Table 2: Clinical chemistry parameters measured

Serum total protein (TP)	Serum albumin (ALB)
Serum lactate dehydrogenase (LDH)	Serum aspartate aminotransferase (AST)
Serum alanine aminotransferase (ALT)	Serum alkaline phosphatase (ALP)
Serum urea nitrogen (BUN)	Serum creatinine (CREA)
Serum uric acid (UA)	Serum sodium (NA)
Serum potassium (K)	Serum creatinine phosphokinase (CPK)
Serum amylase (Amyl)	-

iv. Normal range (Reference value) for serum chemistries

K ref value = 3.7-5.2 mmol/l, Na ref value = 135-145 mmol/l, BUN ref value = 6-20 mg/dl), CREA ref value = 0.6-1.3 mg/dl, UA ref value = 3.5-7.2 mg/dl, ALB ref value = 34-54 g/l , TP ref value = 60-859/l, ALP ref value = 55-142 U/l, AST ref value = 8-40 U/l, ALT ref value = 7-55 U/l, CPK ref value = 38-176 U/l, LDH ref value = 200-450 U/l), AMY ref value = 40-140 U/l.

v. Statistical Analysis

All data are reported as the mean ± S.D. Statistical analysis was performed using SPSS statistics 17. The results were compared by paired t-test. The results with a valueof $p<0.05$ were considered significant.

3. Results

Tables 3-5 show the effects of studied plants on serum clinical chemistry parameters. At the sixth day of administration (*i.e.*, one day following the last dose of day five) *S. triloba* caused a significant increase in serum potassium and uric acid and a significant decreasein serum BUN and lactate (LDH) dehydrogenase. *Z. officinale* caused a significant decrease in serum potassium and BUN and a significant increase in serum creatinine phosphokinase (CPK). *O. syriacum* caused a significant decrease in serum BUN and lactate dehydrogenase (LDH) and a significant increase in serum alkaline phosphatase. *V. triphylla* caused a significant decrease in serum BUN and creatinine and significant increase in serum uric acid. paracetamol caused a significant increase in serum potassium and albumin and a significant decreased in serum creatinine, uric acid and creatinine phosphokinase (CPK). *R. officinalis* had no significant effect on the levels of tested biochemical parameters. However, the effects of tested plants on serum biochemical parameters were all within the known normal ranges of these parameters. However, serum Na, AST and ALT were not affected by any of tested plants.

Table 3: The following parameters were affected by the given medicinal plants. Each value represents the mean value ± SD, (n = 8-10),*$p<0.05$, compared to 0 time administration

	K			BUN			CREA		
	0 time	1 h	Day 6	0 time	1 h	Day 6	0 time	1 h	Day 6
Origanum syriacum	4.2 ± 0.43	4.4 ± 0.27	4.4 ± 0.25	15.4±3.8	14.3 ± 3.8*	11.2± 2.1*	0.78 ± 0.18	0.73 ± 0.17	0. 73 ± 0.0.14
Salvia triloba	4.0 ± 0.47	4.0 ± 0.39	4.3 ± 0.3*	14.7±4.7	14.1 ± 4.7*	11.6± 3.7*	0.71 ± 0.20	0.70 ± 0.19	0.69 ± 0.19
Verbena triphylla	4.38 ± 0.40	4.4 ± 0.21	4.34 ± 0.38	13.5±3.5	13.0 ± 2.8	9.7± 2.0*	0.74 ± 0.13	0.72 ± 0.13	0.65 ± 0.16*
Zingiber officinale	4.3 ± 0.47	4.3 ± 0.53	4.0 ± 0.26*	17.9±4.5	16.6 ± 4.5*	13.5± 3.6*	0.67 ± 0.14	0.67 ± 0.13	0.62 ± 0.12
Rosmarinus officinalis	4.4 ± 0.39	4.6 ± 0.35	4.4 ± 0.29	12.6±2.2	12.6 ± 1.5	10.2± 1.9	0.78 ± 0.20	0.78 ± 0.21	0.76 ± 0.26
Paracetamol	4.3 3 ± 0.42	4.49 ± 0.54	4.72 ± 0.30*	12.6±3.4	12.8 ± 3.6	15.0± 5.1	0.86 ± 0.16	0.94 ± 0.20	0.82 ± 0.18*

Table 4: The following parameters were affected by the given medicinal plants. Each value represents the mean value ± SD, (n = 8-10), *$p<0.05$, compared to 0 time administration

	U.A.			ALP			CPK		
	0 time	1 h	Day 6	0 time	1 h	Day 6	0 time	1 h	Day 6
Origanum syriacum	5.0 ± 1.1	5.0 ± 1.0	5.0 ± 1.0	67.6 ± 24.0	65.9 ± 21.2	70.6± 23.2*	100.7 ± 31.2	106.8 ± 34.8	121.7 ± 57.2
Salvia triloba	3.95 ± 1.7	3.90 ± 1.7	4.27 ± 1.8*	98.5 ± 64.8	97.2 ± 64.8	96.1± 61.0	100.0 ± 58.4	102.9 ± 59.0	118.7 ± 81.0
Verbena triphylla	4.92 ± 1.0	5.0 ± 1.0*	5.4 ± 1.3*	112.9 ± 71.5	110.3 ± 67.2	112.0± 78.3	90.5 ± 65.7	93.0 ± 64.4	80.5 ± 35.8
Zingiber officinale	4.6 ± 1.1	4.7 ± 1.1	4.6 ± 0.84	76.1 ± 22.8	75.8 ± 23.0	77.9± 22.8	63.1 ± 23.9	67.6 ± 22.6*	82.7 ± 32.5*
Rosmarinus officinalis	5.4 ± 1.8	5.4 ± 1.7	5.6 ± 1.8	130.2 ± 86.9	126.8 ± 84.0	126.3± 82.8	124.0 ± 71.8	121.1 ± 64.8	121.0 ± 50.0
Paracetamol	6.3 ± 2.2	6.4 ± 2.0	5.9 ± 2.3*	102.1 ± 30.6	103.8 ± 32.5	98.4± 32.4	194.6 ± 266.8	179.2 ± 231.5	100.9 ± 73.7*

Table 5: The following parameters were affected by the given medicinal plants. Each value represents the mean value ± SD, (n = 8-10), *$p<0.05$, compared to 0 time administration

	LDH			ALB			TP			AMYL		
	0 time	1 h	Day 6	0 time	1 h	Day 6	0 time	1 h	Day 6	0 time	1 h	Day 6
Origanum syriacum	350.5 ±54.5	350.2 ± 66.5	322.5 ± 39.9*	46.6 ± 3.8	45.9 ± 3.9	47.7± 4.0	77.3 ± 6.1	75.8 ±5.4	80.2 ± 6.4	58.1 ± 12.8	55.9 ± 13.4	63.1 ± 16.0
Salvia triloba	355.2 ±38.5	346.1 ± 37.4	318.3 ± 40.5*	47.0 ± 3.5	46.6 ± 3.0	46.2± 3.6	80.0 ± 4.6	79.3 ±4.7	79.8 ± 3.0	67.4 ± 20.2	65.3 ± 16.3	66.8 ± 19.3
Verbena triphylla	307.3 ±48.0	317 ± 48.2	304.4 ± 39.7	45.2 ± 2.2	44.6 ± 2.5	46.6± 3.8	77.6 ± 3.9	76.1 ±2.1	79.7 ± 4.4	46.8 ± 15.2	45.9 ± 14.7	43.3 ± 16.6
Zingiber officinale	375.0 ± 48.7	371.9 ± 42.6	370.5 ± 37.4	44.8 ± 2.8	45.4 ± 2.2	44.5± 2.3	77.7 ± 4.9	78.1 ±3.6	77.9 ± 4.9	57.3 ± 14.3	55.7 ± 13.7	55.8 ± 15.8
Rosmarinus officinalis	403.5 ±105.9	374.6 ± 79.7	358.9 ± 66.9	47.2 ± 4.6	45.3 ± 3.5	46.6± 3.4	79.4 ± 6.7	77.4 ±4.8	81.5 ± 5.5	51.2 ± 16.3	49.3 ±14.1	50.2 ± 15.0
Paracetamol	388.0 ±48.7	381 ± 46.3	367.6 ± 43.5	46.3 ± 4.0	46.2 ± 1.6	49.3± 3.4*	81.6 ± 5.4	81.6 ±3.1	82.6 ± 3.2	52.8 ± 9.7	54.2 ±10.7	56.5 ± 8.9

Table 6: The following parameters were not affected by the given medicinal plants. Each value represents the mean value ± SD, (n = 8-10).

	AST			ALT			Na		
	0 time	1 h	Day 6	0 time	1 h	Day 6	0 time	1 h	Day 6
Origanum syriacum	21.6 ± 11.2	22.4 ± 10.9	21.2 ± 6.3	21.5±16.4	21.9 ± 16.1	20.6± 12.3	145.1 ± 1.4	144.3 ± 1.6	146.0 ± 2.0
Salvia triloba	23.0 ± 6.0	22.7 ± 7.4	22.3 ± 8.0	26.2±16.3	26.2 ± 17.5	26.2± 18.3	144.6 ± 1.6	145.6 ± 1.0	145.6 ± 3
Verbena triphylla	15.8 ± 5.7	16.2 ± 5.0	16.4 ± 5.4	17.4±13.3	17.5 ± 14.1	18.9± 15.7	146.0 ± 2.2	144. ± 1.2	145.4 ± 1.7
Zingiber officinale	22.8 ± 19.0	23.3 ± 17.6	19.5 ± 6.7	22.9±26.8	23.5 ± 26.6	19.6± 13.0	144.9 ± 1.9	143.8 ± 1.6	145.5 ± 1.3
Rosmarinus officinalis	25.5 ± 6.7	25.2 ± 7.2	24.0 ± 5.7	27.6±15.6	26.7 ± 14.1	27.2± 16.7	148.1 ± 2.3	148.5 ± 1.5	147.9 ± 4.8
Paracetamol	26.1 ± 8.7	25.9 ± 7.6	24.1 ± 7.5	38.9±28.3	37.9 ± 26.6	36.3± 23.8	146.0 ± 2.8	144.5 ± 2.1	146.5 ± 2.0

4. Discussion

Many studies reported that collective use of tea with related polyphenols and market-based drugs can ameliorate the treatment way for the disease specifically which are caused by the microorganisms and other toxicants (Sanlier *et al.*, 2018). Study by Toda *et al.* (1989) reported the daily moderated consumption of tea can kill many microbes like *Staphylococcus aureus, Vibrio parahemolyticus, Clostridium perfringens, Bacillus cereus, Pleisomonas shigelloides,* as tea contains 30 to 4 % of water extractable polyphenolic compound (Toda *et al.*, 1989). Apart from that this herbal therapy is also found to be effective equally with the normal analgesic drugs (Chevallier, 2016; Zhu *et al.*, 2008). The herbal therapy is useful for lowering the side effects of the commercially available medicines, and therefore, it can be used as potential treatment of the normal analgesic symptoms for which people used take commercial medicine without prescriptions. The four most abundantly found polyphenolic compounds; epigallocatechingallate (EGCG), epicatechingallate (ECG), epigallocatechin (EGC) and epicatechin (EC) are significantly recorded in tea especially green tea extract as reported in study of Diane *et al.* (2007). In other studies, herbal amalgam of commercial drug tamoxifen and epigallocatechingallate (EGCG) is used as the effective induced apoptotic agents in comparison to the separate one against cancer cells (Chisholm *et al.*, 2004).

In the present study, although the results obtained show some significant increase in some clinical chemistry parameters and some even decreased as recorded in serum when the effect of tested plants were recorded, but these changes were minimal and did not exceed the known normal ranges for these parameters.

Therefore, it is important for future studies to test the effects of these herbal extracts on laboratory methods by direct addition of these extracts to test tubes along with the serum samples. The present study is involving a small number of participants for a short period. Thus, further studies may be needed to clarify the effects of long-term use of these herbs and the related mechanisms on laboratory testing on large sample size.

A small sample size may make it difficult to determine if a particular outcome is a true finding and it considered as one of the study limitations.

5. Conclusion

Since the present study was performed on healthy individuals, one could speculate that the altered laboratory test results by a given herb could be considered as a beneficial effect and/or a side/adverse effect. This phenomenon was obvious in the present study with some tests, showing a beneficial effect of reducing some blood parameters such as BUN and CREA.The effects of tested herbs on the following tests; increased UA, ALP, CPK, ALP, ALB, TP and AMYL and decreased LDH activity cannot be explained as neither positive or negative effects, but overall speaking they should be considered as confusing effects that could lead to confusion in patient's diagnosis and/or treatment.

From our study, it is speculated that herbal plants and their extract are equally beneficial as the commercial drugs but with least side effects.

Ethics statement

This study was carried out in compliance with the ethical principles outlined in the Helsinki Declaration of 1964. Prior to participating in the study, each individual subject gave their informed permission.

Conflict of interest

The author declares no conflicts of interest relevant to this article.

Contributions of the authors

NA designed the study and performed data collection, processing, and analysis.

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