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Impact of *Foeniculum vulgare* Fortified Diet on Coagulation Profile and Some Biochemical Parameters

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Authors' contributions

This work was carried out in collaboration among all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author RI conceptualized, reviewed and edited. Author FH managed the analyses of the study. Author QUAB managed the literature searches. Author AA supervised. Author AA verified the analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Coagulation profile shows the clotting ability of blood. Biochemical tests indicate health status of vital organs such as liver, heart and kidneys. Herbal products are being assessed for their role in affecting these parameters. We evaluated role of *Foeniculum vulgare* incorporated diet on coagulation profile and some important biochemical parameters.
Study Design: Laboratory centred randomized controlled trial.
Place and Duration of Study: Pharmacology Department of University of Karachi, Karachi between June 2018 and September 2018.

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Methodology: After selecting 30 healthy rabbits of either sex, we placed them in three groups; Control, 2% *Foeniculum vulgare* and 4% *Foeniculum vulgare* group. Control group was given standard diet whereas; 2% and 4% *Foeniculum vulgare* groups were maintained on standard diet containing 2% and 4% *Foeniculum vulgare* crushed seeds. Coagulation profile and some biochemical parameters were done after interval of a month, for two months.
Results: Platelet count and fibrinogen increased while activated partial thromboplastin time (APTT) levels decreased in both the study groups animals as compared to control, while blood urea nitrogen (BUN), creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) elevation was noted both *Foeniculum vulgare* groups but within normal range.
Conclusion: *Foeniculum vulgare* may have some role in affecting coagulation and biochemical profile These parameters, however, need clinical trial to validate reliability.

Keywords: Activated partial thromboplastin time; blood urea nitrogen; creatinine phosphokinase; Foeniculum vulgare; lactate dehydrogenase.

1. INTRODUCTION

Coagulation disorder is usually presented with excessive bleeding as a symptom, especially as heavy menstrual flow in women [1]. This bleeding could be an indication of a bleeding disorder, thus, requires further investigation. Prevalence of bleeding vary according to various studies, though it is found to be a common symptom [2]. Platelet dysfunction (PDF) is thought to be a common cause of menorrhagia in women [3] could be up to 30% [4]. Fibrinogen is necessary for clot formation as well as platelets. Both these elements that is fibrinogen as well platelets count and function have a major role in coagulation disorders [5]. Creatinine levels and blood urea nitrogen are indicators of renal function [6]. Moreover elevated blood urea nitrogen could be an indicator of acute coronary syndrome [7]. The ratio of these two biochemical products of protein metabolism also point towards health status of heart failure patients [8,9]. Lactate dehydrogenase is an enzyme required for the conversion of pyruvate to lactate in anaerobic environment as well as indicator of liver function and it has some role in prognosis of various carcinomas in body [10-12]. Elevated creatinine phosphokinase level is indication of rhabdomyolosis [13]. Increase in levels of this biochemical parameter points towards injury to muscle membrane releasing myoglobin in blood which may negatively affect kidney function [14].

Herbal therapy has been proven of possessing protective role against elevation of the above mentioned biochemical parameters. The fennel (Botanical name: *Foeniculum vulgare* Mill, family Umbelliferae) is a known annual, biennial or perennial aromatic plant, according to the variety, has been well known since ages in Asia Minor, Europe and Mediterranean region. Almost all parts of this plant like fruits (seeds), leaves, and shoots are edible. *Foeniculum vulgare* fruits are oblong, curved or straight and are of greenish or yellowish brown colour. Volatile constituents of fennel seed consists of transanethole, fenchone, methylchavicol, limonene, α- pinene, camphene, β-pinene, β-myrcene, α- phellandrene, 3-carene, camphor, and cisanethole [15-17].

Aim of this study was to assess the effects of *Foeniculum vulgare* incorporated diet on coagulation profile and serum levels of some biochemical parameters.

2. MATERIALS AND METHODS

2.1 Study Design

This study was a laboratory centered randomized controlled trial conducted in the Pharmacology Department of University of Karachi. The ethical standards of the study were in line with the Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education issued by the New York Academy of Sciences Adhoc Committee on Animal Research and the study protocol was approved by Board of Advanced Studies and Research (BASR), University of Karachi, Resol. No. 10(P)14 [16].

2.2 Herb Material

Foeniculum vulgare dried fruits were bought from a local departmental store and identified from the Pharmacognosy Department, Faculty of Pharmacy and Pharmaceutical Sciences University of Karachi, and assigned voucher no. FVF-02-15/17.2.2 [17].

2.3 Animals

Thirty, healthy, adult, albino rabbits (weight 1500-2000 gram) belonging to either sex, were taken from the Animal house of Pharmacology

department of University of Karachi. General health of all selected rabbits was checked during acclimatization period of a week, especially observing and noting for sign of diarrhea, hair loss, lack of activity and swelling. Animals were kept in transparent cages under controlled temperature of 23 ±2°C. Specific diet and water was provided ad libitum for 2 months. Rabbits were divided equally in 3 groups, Group 1 being the Control group, Group 2 (2% *Foeniculum vulgare*) and Group 3 (4% *Foeniculum vulgare*). Control rabbits were given standard diet, while, rabbits of group 2 and 3 were fed on 2% and 4% *Foeniculum vulgare* fruits incorporated diet, respectively.

2.4 Sample Collection

After a month's interval 2 ml blood was collected twice, in K3-EDTA tubes for platelet count, and for coagulation profile blood was collected in test tubes containing 3.2% buffered trisodium citrate [18]. For estimation of prothrombin time standard reagent kits of Human Germany were used and analysed by Humaclot duo Coagulation analyser (Model no.18650, human Germany) [19,20].

Plasma fibrinogen estimation was done by employing hemostat fibrogen method (manual and automated determination of Plasminogen fibrinogen) as documented by Clauss [21]. The basis of this test is that 1:10 pre-diluted plasma thrombin is added in optimal quantity. Time taken by plasma to clot in the given sample has inverse relationship to concentration of fibrinogen [22]. Whereas, activated partial thromboplastin time (APTT) is conducted by adding an activating agent (phospholipid) and calcium to the citrated, platelet-poor plasma. The time to form fibrin clot was noted and the resulting value was matched either to the result of a normal control plasma sample done simultaneously, or to a normal value distribution [18,23].

2.5 Statistical Analysis

All values were statistically analyzed using SPSS 17.0. All readings were taken as mean±SD and compared by Analysis of variance (ANOVA) using post hoc Tukey's test. *P* value = 0.05 was considered significant, *P* value = 0.01 was considered very significant and *P* value = 0.001 was considered as highly significant .

3. RESULTS

It is evident from results that platelet count increased in both *Foeniculum vulgare* fortified diets fed animals, while fibrinogen levels increased remarkably only in 4% *Foeniculum vulgare* group. In contrast APTT decreased in both study groups (Table 1).

Biochemical parameter assessment revealed slight lowering of serum creatinine levels while BUN values increased in both treated groups. Serum levels of CPK and LDH decreased in 2% *Foeniculum vulgare* group while increased in 4% *Foeniculum vulgare* group (Table 2).

Table 1. Effect of *Foeniculum vulgare* diet in different ratio on coagulation profile

Parameter	Groups	Day 30	P value	Day 60	P value
Platelet Count (10^9/L)	Control group	285.40±1.25	0.001[a]	292.20±2.02	0.001[a]
	2% *Foeniculum vulgare* group	341.99±2.28		794.47±1.71	0.001[c]
	4% *Foeniculum vulgare* group	313.74±1.72[!]	0.001[a] 0.001[b]	570.73±1.66	0.001[a] 0.001[b] 0.001[c]
Fibrinogen (g/L)	Control group	2.3±1.19	NS	2.43±1.06	NS
	2% *Foeniculum vulgare* group	2.81±1.08		2.78±1.50	
	4% *Foeniculum vulgare* group	4.05±1.41	0.009[a]	3.35±1.30	NS
Activated Partial Thromboplastin Time (seconds)	Control group	34.78±1.36	0.01[a]	34.39±3.32	0.01[a]
	2% *Foeniculum vulgare* group	32.07±2.28		30.03±2.55	
	4% *Foeniculum vulgare* group	23.22±1.20	0.001[a] 0.001[b]	28.54±1.4	0.001[a] 0.001[c]

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)
[a]P -value in comparison to control
[b]P -value among the study groups
[c]P -value within the study group

Table 2. Effect of *Foeniculum vulgare* diet in different ratio on biochemical parameters

Parameters	Groups	Day 30	P-value	Day 60	P value
Creatinine (mg/dl)	Control group	1.07±0.67	0.110[a]NS	1.17±0.71	0.586[a]NS
	2% *Foeniculum vulgare* group	0.77±0.12		0.84±0.11	
	4% *Foeniculum vulgare* group	0.72±0.16	0.051[a]NS 0.935[b]NS	1.15±0.27	0.527[a]NS
Blood Urea Nitogen (mg/dl)	Control group	27.82±1.20	0.001	30.14±1.19	0.001[a]
	2% *Foeniculum vulgare* group	39.62±2.61		35.35±1.24	0.001[b]
	4% *Foeniculum vulgare* group	37.91±1.86	0.001	42±2.34	0.001[a] 0.001[b] 0.01[c]
Creatinine Phophokinase (mg/dl)	Control group	-		311.46±2.31	0.001[a]
	2% *Foeniculum vulgare* group	-		250.02±2.06	
	4% *Foeniculum vulgare* group	-		542.78±2.17	0.001[a] 0.001[b]
Lactate dehydrogense (mg/dl)	Control group	-		212.81±0.80	0.05[a]
	2% *Foeniculum vulgare* group	-		207.34±0.97	
	4% *Foeniculum vulgare* group	-		251.81±0.26	0.001[a] 0.001[b]

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)
[a]P-value in comparison to control
[b]P-value among the study groups
[c]P -value within the group

4. DISCUSSION

Blood coagulation profile is a basic criterion with respect to well-being of a patient. Hypercoagubility or hypocoagubility level in patient is a red sign. Thus, we assessed the impact of *Foeniculum vulgare* incorporated diet on coagulation profile in rabbits for two months.

This study showed significant elevation in platelet count of rabbits of both the treated groups which could be due to membrane stabilizing potential of *Foeniculum vulgare*. This is attributed to lowering of adverse effects caused by free radicals on cell membranes stability; therefore, elevation in cell count is noted. Change in fibrinogen levels was found to be insignificant except in 4% *Foeniculum vulgare* group which increased after a month.

Mansouri and colleagues noted in their study that, *Foeniculum vulgare* significantly elevated coagulation time [24]. Literature research revealed that compounds like coumarin, flavonoids, phenylpropanoid, and phenolic have anti-thrombotic and anti-platelet properties. Based on various trials, *Foeniculum vulgare* possess atypical composition, vasodilatory action and anti-platelet potential [25]. The phenylpropanoid compounds present in this herb exhibited the marked anti-platelet effect caused by inhibition of arachidonic acid and Thromboxane A and ADP [26].

Liver being the major organ of metabolism and detoxification has a basic role in converting various chemical compounds. As it is responsible for blood purification by transforming harmful compounds to harmless substances, it is also prone to injury by these toxic chemicals. The liver disorders are thought to be important health problems around the world. The conventional medical therapy is currently insufficient to handle this issue resulting in high morbidity and mortality. The drugs presently available for chronic liver disorders have unwanted effects [27]. Thus, studies are being conducted to find natural antioxidants possessing hepatoprotective action.

In this study serum lactate dehydrogenase levels were estimated for assessment of any toxic effects of *Foeniculum vulgare* containing diet in two ratios in rabbits. There was no significant difference noted among control and study groups indicating hepatic safety of this herb. An earlier study showed the hepatoprotective effect of *Foeniculum vulgare* against hepatotoxic agents such as diethyldithiocarbamate [28]. Another study documented that contituents such as D-

limonene and β-myrcene found in this herb elevate glutathione concentration in liver which is required by many enzymes that assist in formation of disulphide bonds of many proteins [29]. Hepatoprotective effects of *Foeniculum vulgare* could be attributed to its antioxidant potential and/or inhibitory effect on cytochrome and synthesis of oxon [30]. Devika and coworkers revealed the hepatoprotective impact of *Foeniculum vulgare* methanolic extract against paracetamol induced toxicity in rodents [31]. Similar study conducted by Ghanem et al revealed hepatoprotective potential of *Foeniculum vulgare* [32].

Nephrotoxicity is characterized by alterations in functions like inhibition of protein synthesis, decrease in glutathione depletion, lipid peroxidation and mitochondrial injury. Damage caused by oxidative stress is thought to be one of the major mechanisms leading to nearly all chronic nephrogenic pathologies [33]. Many herbs have been utilised for the treatment of kidney failure in traditional medicine around the world [34].

To assess renal function, serum creatinine, blood urea nitrogen and creatinine phosphokinase were estimated, in rabbits fed on 2% and 4% *Foeniculum vulgare* diet. Serum creatinine declined in both the treated groups as compared to control. A significant difference was noted with respect to BUN and creatinine phosphokinase in both study groups but the results of remained within the normal range. These findings suggest possible nephroprotective property of the study herb. Our results are in line with a study of El-Masry which demonstrated nephroprotective effect of *Foeniculum vulgare* against lead induced neprotoxicity [35]. Similar renal protection was noted in another study using gentamicin as nephrotoxin and *Foeniculum vulgare* as protective agent [36]. Same effect was seen with 2% and 4% *Foeniculum vulgare* incorporated diet in our study.

5. CONCLUSION

The anticoagulant, hepatoprotective and nephroprotective actions noted in this study should be evaluated by clinical study as this herb could be a low cost alternative to presently available medicines.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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