The Effects of Oregano Oil on Fungal Infections Associated with Metabolic Syndrome

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This study aims to compare the evolution of mycosis associated with metabolic syndrome under allopathic treatment compared to phytotherapy using oregano essential oil. The study was conducted over a period of 6 months, on a total of 72 patients diagnosed with fungal infections associated with metabolic syndrome. The patients were divided into 3 groups, depending on the administered treatment: group 1: 24 patients who received allopathic treatment; group 2: 24 patients who received oregano oil treatment; group 3: control, which did not undergo any antifungal treatment. All three groups were subjected to specific diet therapy for mycosis. The patients were initially evaluated at 10 days after the begining of the treatment (to track mycotic disease evolution in the acute phase), at 60 days (to evaluate the recurrence of mycoses) and at 180 days to track recurrent disease. Most infections were acute (77.78%), the chronic ones representing only 5.56% of cases. There were also 12 cases with recurrent infections (16.67%), out of which 6 cases (8.33%) had previously shown resistance to Nystatin. In the 72 cases there was a sensitivity of 100.00% for oregano oil and Ketaconazolum, insignificantly higher than for Myconazolum (97.22%, p=0.157), but significantly higher than for Clotrimazolum and Nystatinum (94.44%, p=0.0437), Variconazole and Fluconazole (88.89%, p=0.0038) and Itraconazole (86.11%, p=0.0011). The results of this study showed an increased efficiency of oregano oil on the symptomatic and paraclinical improvement of mycotic infections in the study, both on short term and on long term, which was completed with high tolerability.

Keywords: Oregano oil, metabolic X syndrome, fungal infections

Metabolic X syndrome is one of the most common diseases of our century. Chaotic feeding, irregular meal timing combined with chronic stress are factors that often cause intestinal dysbiosis [1]. Dysbiosis in turn, favors the appearance of metabolic X syndrome, which entails a number of diseases such as atherogenic dyslipidemia, cardiovascular disease, hyperuricemia, diabetes, visceral adiposity, endothelial dysfunction, hypertension and hypercoagulability [2-5]. Metabolic syndrome manifestations are various, inconsistent, with variable frequency and can be inflammatory, gastrointestinal, mood disorders, exhaustion, anxiety etc. [6].

Fungal infections are commonly associated with metabolic dysfunctions, including metabolic syndrome [7]. In their pathogenesis, an important role is played by the disruption of carbohydrate metabolism, atherosclerosis, microangiopathy and neuronal degeneration, dysfunctions associated with acidosis generated by unbalanced blood glucose [7,8]. Other risk factors such as type II diabetes, dyslipidemias, visceral adiposity and a pro-inflammatory and procoagulant systemic state, including lifestyle (diet, alcohol consumption, smoking and physical activity) can cause a state of acidosis in the body which increases the risk of occurence and aggravation of mycosis [9].

According to the Board of the European Association for the Study of Diabetes (EASD) [10], over 30% of patients with diabetes and metabolic syndrome have a complication of this disease at the skin level. These infections lead to increased morbidity (mucormicosis) especially in diabetes and uncontrolled metabolic syndrome [11-13]. Most common are Candida albicans infections, which mostly affect the skin, nails, interdigital spaces, but also the scalp and mucous membranes of the mouth and vaginal mucosa [14]. Medical treatment (allopathic) may be local or systemic, it is

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administered for a long time and has a number of side effects that considerably influence the adherence to treatment and, implicitly, its effects and disease evolution. In particular, adverse effects in the liver may worsen the course of the disease. For these reasons, alternatives to allopathic treatment, with high efficiency and less adverse effects are being investigated more and more.

The essential oregano oil has been tested in several clinical trials, revealing intense bactericidal and fungicidal activity towards various microorganisms due to the phenolic compounds, carvacrol and thymol: 2-methyl-5-isopropylphenol, 3-methyl-6-isopropylphenol (Fig. 1) [15].

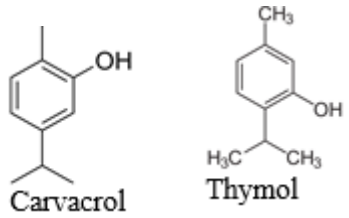

Fig.1. Chemical structure of phenolic compounds with antibacterial action: carvacrol, thymol

The mechanism of action of timol and carvacrol is probably related to their effect on the interruption of bacterial and fungal membrane integrity, which further affects the pH of homeostasis and the balance of inorganic ions. It also acts by interfering with biochemical mechanisms, inhibiting electron transport, proton translocation and oxidative phosphorylation stages [16]. On Candida, it is believed to act by destroying ergosterol biosynthesis and fungal membrane integrity [16]. The timol sulfate metabolite, with antimycotic efficiency clinically proven (*in vivo* and *in vitro*), has been detected in the blood after a 10.2 hour half-life, with a plasma concentration of 93 ng/mL, after oregano oil administration. This result has led to an increasing interest in the use of oregano oil as an alternative treatment with antimycotic potential [17].

This study looked into the effects of oregano oil compared to allopathic medication on pathogens involved in fungal infections associated with metabolic syndrome.

Experimental part

Study design

The study was conducted over a period of 12 months, on 72 patients diagnosed with fungal infections associated with metabolic syndrome, respecting the principles of research on human subjects, with the approval of the Ethics Commission of the Faculty of Medicine and Pharmacy Oradea. Each patient included in the study signed an informed consent form. Children over 4 years and adults under 61 were included, with HOMA index above 2.5 and BMI over 25. Patients allergic to treatments used in the study and/or those with unstabilized chronic disease have been excluded. Patients were divided into 3 groups, depending on the clinical characteristics, medical history and availability to follow treatment: group 1 included 24 patients who received allopathic treatment, group 2 included 24 patients treated with oregano oil and control group 3, which did not follow any antifungal treatment. All three groups were subjected to specific diet in mycosis, established by the nutritionist.

The evaluation was initially done at 10 days after the begining of the treatment, to track the evolution of mycosal disease in the acute phase, at 60 days to evaluate mycotic recidivation and at 180 days, for recurrent disease follow-up. The sensitivity of pathogens to the treatment and the evolution of mycoses were monitored in a comparative manner, depending on the therapy administered.

Treatment used in the study

Allopathic treatment was recommended by the treating physician according to the fungigram and consisted of oral administration of nistatin, fluconazole and itraconazole, and locally ketoconazole, miconazole and clotrimazole, administered according to the individualized treatment regimen (maximum dose per age and kilogram body weight).

Phytotherapy was performed with oregano P73 – 71% volatile oil, 0.8 g of oil administered internally or externally (equivalent to 2 drops) with 0.568 g of active substance: phenol (44%) - thymol and carvacrol isomer; bi- and tricyclic sesquiterpene (12.5%); free alcohols composition $C_{10}H_{18}O$ (15%); tannins; ascorbic acid (in leaves up to 565 mg%), flavonoids. Diluted or treated with water (aromatic water) it was used in children aged 4-12 years.

Biochemical determinations

Depending on the clinical manifestations, biochemical samples were taken, laboratory tests that confirmed the presence of fungal infection and the fungigram were performed. The method used to make the antifungigram is the Kirby-Bauer standardized diffusion method. An amount of antimycotic substance is deposited on the surface of an agarized culture medium pre-seeded with the tested fungus. The diffusion of the antimycotic substance occurs and the growth of fungi is observed. In areas where the antimycotic has a higher concentration than the minimum inhibitory concentration (MIC), the fungus does not grow. The circumference of the inhibition zone is established prior to installing the exponential phase of the culture, where the diameter of the area is inversely proportional to the CMI. According to the protocol, the antimycotic standards used were nystatinum, ketoconazolum, itraconazole, variconazole, myconazlum, clotrimazole and fluconazole; a standard of oregano oil was prepared, impregnating a standard size filter paper set with 71% oregano oil, which was inoculated into the culture medium.

Statistical analysis

The optimum size of the grouping interval can be determined using the empirical formula:

$$1 = \frac{X_{max} - X_{min}}{1 + 3{,}322 \lg n}$$

where X_{max}, X_{min} represent the highest and lowest value of the score, *n* is the number of subjects in the test group and *1* is the optimal size of the grouping interval.

For all samples, susceptibility to oregano oil was tested. Thus, the rough results according to the diameter obtained from the oregano oil fungigram in the three groups are presented in Table 1.

Tabel 1
THE DIAMETER OBTAINED FROM THE ANTIFUNGIGRAM OF OREGANO OIL IN THE 3 GROUPS (IN MILLIMETERS), FOR ALL PATIENTS

Group 1							
33	40	42	47	65	50	30	53
37	36	46	34	39	41	32	43
37	39	37	35	49	52	44	39
Group 2							
39	35	49	52	44	39	43	32
41	39	34	46	36	37	53	30
30	50	39	65	47	42	40	33
Group 3							
42	47	37	39	46	34	41	37
36	37	47	43	42	41	39	41
42	34	41	39	43	37	42	46

Results and discussions

Demographic and clinical characteristics of patients

In the study, adult female patients prevailed. Most infections were acute (77.78%), the chronic ones representing only 5.56%. There were also 12 cases with recurrent infections (16.67%), of which, 6 cases (8.33%) had previously shown resistance to Nystatin. Most cases were vaginal discharge (33.33%), followed by nasopharyngeal secretion (27.78%) and stool fungal culture (22.22%). Nearly 98% of the samples revealed *Candida albicans* (97.22%); only two samples had *Aspergillus* (2.78%) (Table 2).

Tabel 2
DISTRIBUTION OF CASES ACCORDING TO CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

Characteristics			**Group 1**	**Group 2**	**Group 3**
	No.	%			
Age C/A (years)	26/46	36.11/63.89	9/15	5/19	11/13
Sex M/F	25/47	34.72/65.28	8/16	9/15	8/16
Type of infection					
Acute infections	56	77.78	87.5	70.83	75.00
Chronic infections	4	5.56	4.16	4.16	8.33
Recurrent infections	12	16.67	8.33	25.00	16.66

Material collected					
NPS (nasopharyngeal secretion)	20	27.78	29.16	20.83	33.33
SFC (stool fungal culture)	16	22.22	25.00	12.5	29.16
VD (vaginal discharge)	24	33.33	33.33	37.5	29.16
NS (nasal secretion)	2	2.78	4.16	4.16	-
Uroculture	2	2.78	-	4.16	4.16
Mycological exam	6	8.33	4.16	16.66	4.16
Spermoculture	2	2.78	4.16	4.16	-
Fungal infection					
Aspergillus	2	2.78	4.16	4.16	-
Candida albicans	70	97.22	95.83	95.83	100.00

Sensitivity to treatment

In the 72 cases there was a sensitivity of 100.00% for oregano oil and Ketaconazolum, insignificantly higher than for Myconazolum (97.22%, p=0.157), but significantly higher than for Clotrimazolum and Nystatinum 94.44%, p=0.0437), Variconazole and Fluconazole (88.89%, p = 0.0038) and Itraconazole (86.11%, p=0.001) (Table 3).

Table 3
DISTRIBUTION OF CASES ACCORDING TO THE SENSITIVITY TO MEDICINES IN THE 3 GROUPS

Standards	Group 1			Group 2			Group 3		
	S	I	R	S	I	R	S	I	R
	%								
Oregano oil	100	-	-	100	-	-	100	-	-
Ketoconazolum	100	-	-	100	-	-	100	-	-
Myconazolum	91.66	8.33	-	100	-	-	100	-	-
Clotrimazolum	95.83	4.16	-	95.83	4.16	-	91.66	8.33	-
Nystatinum	83.33	-	8.33	95.83	-	4.16	95.83	-	4.16
Voriconazolum	91.66	-	8.33	92.66	4.16	4.16	83.33	12.5	4.16
Fluconazolum	87.5	-	12.5	91.66	4.16	4.16	87.5	4.16	8.33
Itraconazolum	87.5	-	12.5	83.33	-	16.66	87.5	-	12.5

According to the antimicrogram, the diameter of the antimycotic standards ranges from 32.31 for Clotrimazolum, being the lowest diameter and 41.31 for the oregano oil (Table 4). The mean of the oregano oil diameter is significantly higher than for the other medicines (p <0.0001) (Fig. 2).

Table 4
MEDIUM VALUES OF DIAMETERS

Standards	No. of sensitive cases	Limit Inf. -Sup. (mm)	Diameter (Mean±SD) (mm)
Oregano oil	72	32-65	41.31±5.01
Ketoconazolum	72	32-34	33.04±0.71
Myconazolum	70	32-36	33.54±1.20
Clotrimazolum	68	32-33	32.31±0.59
Nystatinum	68	32-36	33.37±1.09
Variconazolum	64	32-35	33.13±0.89
Fluconazolum	64	32-36	34.28±1.44
Itraconazolum	62	32-36	33.02±0.83

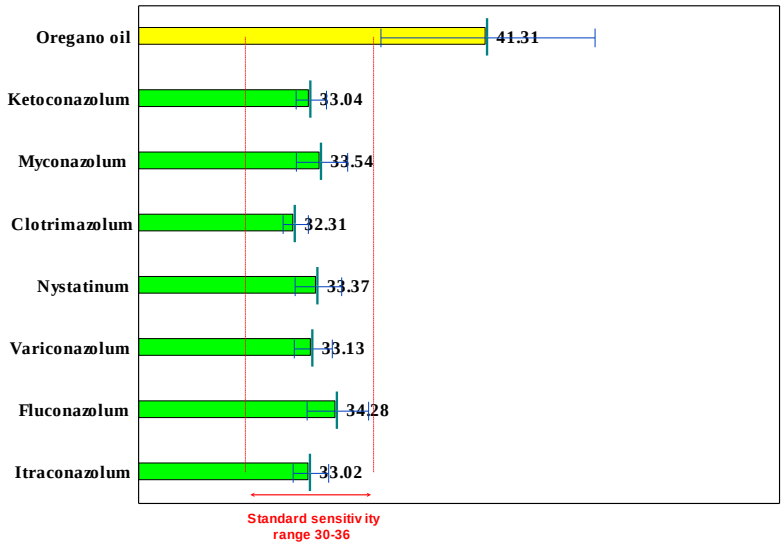

Fig. 2. Average values of diameters

Evolution of mycotic infections

Treatment with oregano oil significantly reduced the symptoms of fungal infection in the doses administered internally, compared to the group receiving only diet therapy. In the case of external administration there was an immediate improvement; in the diluted form or treated with water (aromatic water), the treatment proved efficient at the age of 4-12 years, too. At the 10-day evaluation, there was a favorable progression of the symptoms (symptom disappearance or amelioration), over 90% in the groups with therapy versus 25% in the control group.

There were no significant differences between the two therapies at the 10 day evaluation. The effects of oregano oil treatment were maintained at 60 and at 180 days, respectively, in most patients, unlike the allopathic treatment group where symptomatology returned to a significant number of patients (Table 5).

Table 5
THE EVOLUTION OF FUNGAL INFECTION AT 10, 60, 180 DAYS

Symptoms	**At 10 days**		**At 60 days**		**At 180 days**	
	No.	%	No.	%	No.	%
Group 1						
Absent	7	29.17	9	37.50	11	45.83
Improved	16	66.67	9	37.50	7	29.17
Stationary	1	4.17	-	-	-	-
Worsen	-	-	-	-	-	-
Recurrence	-	-	6	25.00	6	25.00
Group 2						
Absent	9	37.50	7	29.17	3	12.5
Improved	15	62.50	4	16.67	4	16.67
Stationary	-	-	1	4.17	-	
Worsen	-	-	-	-	-	-
Recurrence	-	-	16	66.67	18	75.00
Group 3						
Absent	2	8.33			-	
Improved	4	16.67	6	25.00	7	29.17
Stationary	18	75.00	10	41.67	12	50.00
Worsen	-	-	-	-	1	4.17
Recurrence	-	-	4	16.67	4	16.67

It is more and more necessary to replace the chemical products used as antimicrobial factors in nutrition or in fighting against infections with endogenous microorganisms resistant to synthetic antimicrobial medicines. Eukaryotic organisms cause mycotic infections, their presence being difficult to discover and to administer the adequate treatment unlike in the case of bacterial infections [18]. The difficulty of the treatment lies in the fact that early diagnosis is needed and the available treatment, besides having side effects, is quite limited and various organisms are resistant to medication. Medicines that are very efficient and present low toxicity are required by physicians [19]

A promising alternative to chemicals used for the treatment of mycosis is represented by essential oils (EOs) [20]. EOs obtaines from a large variety of plants and herbs present powerfull antimycotic properties [21,22]. The microbial development as well as the biofilm development may be reduced through specific mechanisms using EOs and other phytochemicals [23-27]. Oregano essential oil has a mixture of compounds, very complex, the main components being terpenes usually mono- and sesquiterpenes. EOs compounds and concentration differ according to a great number of factors like: pests, species, geographical location, soil conditions, climatic and growth conditions, harvest season. [28-33]

In our research were analyzed the effects of 71% oregano essential oil on fungal infections in patients with metabolic syndrome. In the case of this product, carvacrol and thymol are major components, together with p-cimen (4-isopropyl toluene) and (+) (-) terpinene, which are precursors in the biosynthesis of thymol and carvacrol. Other bioactive compounds include phenolic acids (caffeic acid, p-coumaric acid, rosmarinic acid), ursolic acid and carnosic, but also a mixture of flavonoids.

In the initial assessment, there were no significant differences between groups in terms of clinical characteristics. It is noted that both oregano oil and allopathic therapy had a beneficial effect on symptomatology. The best results in both treatment groups were seen in the evaluation after 10 days. It was also found that allopathic treatment was slightly more effective than oregano oil in the first 10 days, but recurrence of infections was much more common in this group. The greater tendency to mycosis recurrence following allopathic treatment can be attributed to the resistance acquired against the therapeutic agent [19]

The results of this study confirmed that oregano oil, is a mixture of natural antimycotic compounds efficient against patogenic microorganisms, being considered modern medicine in the treatment of mycotic diseases. The results obtained are supported by the *in vitro* tests, which indicated a sensitivity of 100.00% of the pathogens to oregano oil, and are consistent with the data obtained in other studies [34-38].

Conclusions

Our results confirmed an increased efficiency of oregano oil on the symptomatic and paraclinical improvement of studied mycotic infections, both on short term and on long term, which was completed with high tolerability.

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