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DNA gene expression of *Candida albicans* and the effect of alcoholic extract of some medicinal plants on its virulence factors

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ABSTRACT

Candida albicans infections are often associated with biofilm formation. The expression of the ALS1, CAP1, CAT1, and LIP3 gene families is associated with biofilm growth on mucosal surfaces and with *C. albicans* virulence genes. The present study investigated the efficacy of the alcoholic extract of the medical plant (Mixed Camellia sinensis and Citrus aurantifolia and the extract of Mirabilis jalapa in relation to its antifungal properties against C. albicans and the effect on gene expression of *C. albicans* virulence factors. Twenty samples (swabs) were collected from patients with oral candidiasis; all of the samples tested were positive. *Candida* isolates were cultivated on Sabouraud Dextrose Agar and identified using standard techniques and HiCrome *Candida* medium. It was confirmed by molecular diagnosis and then by measuring the gene expression of virulence genes before and after treatment with selected plant extracts of different concentrations (50%, 75%, 100%, 200%) for both extracts. The Candida gene-expression data indicated that both extracts showed lower expression at the 100% and 200% doses than at the other concentrations.

***Keywords*:** *Candida albicans,* virulence factors, Gene expression, medical plant extract.

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التعبير الجيني للحامض النوويDNA للمبيضات البيضاء *Candida albicans* وتأثير المستخلص الكحولي لبعض النباتات الطبية على عوامل ضراوته

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الملخص

غالبًا ما ترتبط عدوى المبيضات *Candida albicans* بتكوين الأغشية الحيوية. يرتبط التعبير الجيني عن عائلات الجينات ALS1 و CAP1و CAT1 و LIP3 بنمو الأغشية الحيوية على الأسطح المخاطية لجينات عوامل الضراوة لـ *C. albicans* . بحثت الدراسة الحالية في فعالية المستخلص الكحولي النباتي الطبي (خليط شاي الاخضر *Camellia sinensis* و نومي بصرة *Citrus aurantifolia* ومستخلص شب الليل *Mirabilis jalapa*) فيما يتعلق بخصائصه المضادة للفطريات ضد المبيضة البيضاء وتأثيرها على التعبير الجيني لعوامل ضراوة المبيضة البيضاء *C. albicans*. تم جمع عشرين عينة (مسحات) من مرضى داء المبيضات الفموي، وكانت جميع العينات إيجابية. تمت زراعة عزلات المبيضات على وسط سابرود أجار Sabouraud Dextrose Agar وتم تشخيصها باستخدام التقنيات التقليدية وعلى وسط HiCrome *Candida*، وتم التأكد من تشخيص العينة عن طريق التشخيص الجزيئي ومن ثم قياس التعبير الجيني لجينات االضراوة قبل وبعد المعاملة بالمستخلصات النباتية ذات التراكيز المختلفة (50%، 75%، 100%، 200%) لكلا المستخلصين. أشارت نتائج بيانات التعبير الجيني للمبيضات إلى أن مستويات التعبير الجيني للمستخلصين انخفضت عند الجرعات العالية 100 و 200% مقارنة ببقية التراكيز .

INTRODUCTION

Candida is part of the normal flora and is the most widespread species because it possesses multiple virulence factors that enable it to cause infections across various body systems, ranging from superficial infections such as oral infections to systemic infections [(1)]. *Candida albicans* is an opportunistic/pathogenic yeast associated with candidiasis, especially oral candidiasis [(2)]. Generally used antifungal drugs to treat stomatitis, but most of these antifungal drugs can induce side effects, resistance and recurrence [(3)]. The increased prevalence of superficial and systemic infections caused by Candida species has been linked to their resistance to antifungal agents and to the expression of multiple virulence factors following antifungal exposure during antifungal therapy [(4)].

Thus, it is important to understand the virulence and resistance mechanisms associated with these species. Furthermore, understanding how virulence factor genes are expressed and how therapeutic interventions affect their expression may serve as a gauge of treatment efficacy [(5)]. *C. albicans's* pathogenic potential is influenced by the production of proteins necessary for invasion and adhesion. Numerous factors, including the types of proteins in the cell wall and the physicochemical properties of the cell surface, influence adhesion. *C. albicans* adhesins attach to ligands that they recognize, including proteins, fibrinogens, and fibronectins [(6)]. Important phytochemicals and extracts from medicinal plants are widely used to treat a range of illnesses. Many people turn to medicinal plants to treat a variety of fungal infections, either alone or in combination with well-known antifungal medications (7), so plant extracts are used as

potential alternatives to conventional antifungal agents with no side effects and low cost [8].

Camellia sinensis L. (green tea) belongs to the Theaceae family, popularly known as green tea or Indian tea, is the second most popular drink worldwide and used to pharmaceutical and scientific communities, it shows antifungal activity against *Candida* species due to it contains polyphenolic ingredients such as flavonoids and catechins [9], which are antioxidants and inhibitors of lipid peroxidation [10].

Mirabilis jalapa L. belongs to Nyctaginaceae, a perennial herb or undershrub plant with thickened and tuberous roots, and a traditional medication that is used to treat a wide range of illnesses in many regions of the world. *M. jalapa's* tuberous root has long been utilized as an antifungal agent, and the phytochemicals found in plant extracts include triterpene, protein, alkaloid, flavonoid, and steroid, among other active substances [11].

Citrus aurantifolia (Family: Rutaceae) is one of the most important economic plants; yet, prior research suggests that its fruits, not its leaves, are valued more. *Citrus sp*. has specific bioactive chemicals that exhibit antibacterial, antioxidant, anti-cancer, anti-fungal, and depressive properties, along with the ability to combat *Candida* [12].

The present study's focus on how plant extracts influence Candida virulence genes underscores the importance of exploring natural therapies, fostering a sense of purpose in antifungal research.

MATERIAL AND METHODS

Candida albicans Isolation and Identification

For yeast *C. albicans, which is isolated from oral infections, 20 samples (swabs) (10 females and 10 males, aged between 22 and* 35 years) were collected from patients at the College of Dentistry/Tikrit University. It was sub-cultured on Sabouraud-Dextrose Agar (SDA, UK) and then incubated at 37±2ºC for 48h. Then it was cultured on chromogenic Candida agar to confirm identification (13), and a molecular diagnosis was performed using conventional PCR with the ITS1 and ITS4 primers.

Collection of Plant Extract

Alcoholic (ethanol) plant extract powder was obtained from the University of Baghdad/College of Science, prepared and ready for use for *Mirabilis jalapa* plants and a mixture of *Camellia sinensis*)green tea) and *Citrus aurantifolia* extracts. Several concentrations (50%, 75%, 100%, 200%) were prepared from them.

Concentration and Preparation of Stock Solutions

One gram of each powdered extract was weighed and soaked in 10 ml of DMSO (Dimethyl sulfoxide) solvent to a concentration of 200%, from which concentrations of 50%, 75% and 100% were prepared as mentioned below for each of the following groups:

Extract A: A first group consists of a mixture of *Camellia sinensis* .Green tea) and Citrus aurantifolia extracts(. To show that the effect of mixing the two extracts in the current study is better than each one alone, according to previous studies.

Extract B: A second group consists of *Mirabilis jalapa* extracts.

The stock solutions were kept in a dark place between (4-8) ˚C, in sterile containers with tight caps.

Prepare five tubes containing 1.5 ml of yeast culture (*C. albicans)*, then inoculate each tube with 0.5 ml of each concentration of extract A and B (50%, 75%, 100%, 200%), as four tubes for each concentration and one control for each group, which were incubated at 37±2ºC for 48h.

Yeast RNA isolation

The Transzol Up Plus RNA Kit was used, prepared by TRANS and used according to the manufacturer's instructions.

cDNA Synthesis Method

The conversion of single-stranded RNA into complementary DNA strands is necessary for the RT-qPCR method used to assess gene expression. To do this, the TRANS kit was used, which was

prepared by Easy Script First Strand DNA Synthesis Company and used according to the manufacturer's instructions (Table 1, 2).

Table 1: Additions needed to prepare cDNA

Component	Volume IU
RNA	7
Anchored oligo	11
ES Reaction mix	11
Easy Script TR/RT enzyme mix	1µl
Reaction mix	10

Table 2: cDNA interaction program

Step	Time	Temp.	Cycle
Denaturation	15 min	25	1 Cycle
Annealing	15 min	42	
Extension	5 sec	85	

Primers used for gene detection

To identify important genes linked to Candida albicans pathogenicity, initial PubMed searches were conducted. To determine their specificity, four published primers were selected for in vitro testing (Table 3).

Table 3: Primers used in RT-qPCR in the current study

Genes	Primer	T℃	CG %	Product-length	References
ALS1	F - CATCATTGACTCAGTTGT	55.9	38.9	117	(5)
	R - CAGTGGAAGTAGATTGTG	56	44.4		
CAP1	F - AGTCAATTCAATGTTCAAG	55	31.6	87	
	R - AATGGTAATGTCCTCAAG	55.2	38.9		
CAT1	F - GACTGCTTACATTCAAAC	55.1	38.9	117	
	R - AACTTACCAAATCTTCTCA	55.1	31.6		
LIP3	F - TCTCACCGAGATTGTTGTTGGA	65.8	45.5	68	(14)
	R - GTTGGCCATCAAATCTTGCA	63.6	45		

Real-time polymerase chain reaction (RT-qPCR)

TRANS used the Perfect star Green Super Mix kit. The cDNA preparation was initiated differently; the tube holder was restored, and the actual preparation of the element began according to the manufacturer's specifications (Table 4).

Table 4: The RT-qPCR reaction program

Cycle No.	Time/Sec.	Temp.	Phases
Holding stage 1	3 min	94	Enzyme activation (polymerase)
40	15 sec	94	Denaturation
	40 sec	60	Linkage of elongation of beginners for Gene ALS1
	40 sec	60	Linkage of elongation of beginners for Gene CAP1
	40 sec	60	Linkage of elongation of beginners for Gene CAT1
	40 sec	60	Linkage of elongation of beginners for Gene LIP3
95c˚/15sec-60/1min 95c˚/30sec60c˚/15se			Dissociation

RESULTS AND DISCUSSION

Twenty samples, including oral-cavity swabs, were collected from patients at Tikrit University/College of Dentistry. All samples tested were positive (100%) for *Candida albicans, as detected by oral swab*. According to earlier research, approximately 10% of common oral cavity species act as opportunistic Candida pathogens, causing infections such as oral candidiasis [15].

The results of the current study were consistent with several studies to demonstrate the importance of medicinal plants and their extracts as antifungal and antibiofilm agents, as the expression of virulence genes of the yeast *C. albicans* was affected by an increase or decrease in the level of gene expression for virulence factors after treatment with different plant extracts.

The results of Table 5 and Figure 1 showed the effect of the extract of A (Mixed of *Camellia sinensis* and *Citrus aurantifolia)* on increasing gene expression, especially at concentrations of 50% and 75%. Nevertheless, it led to a clear decrease in the expression of virulence factor genes in yeast after treatment with high concentrations of this extract,

particularly at 100% and 200%. The higher the extract concentration, the lower the gene expression relative to the control; a fold change of 1 (16) was observed in their investigation of the effects of C. sinensis, which has the highest chemical content and shares impact similarities with antifungal agents, specifically against oral infections. Certain compounds, such as epigallocatechin gallate, are essential for preventing ergosterol synthesis by interfering with folic acid metabolism, particularly in *Candida albicans* [17].

The results of the current study of the *Citrus aurantifolia* extract were consistent with [18] results in their study on the fungal efficacy tests, which demonstrated that alcoholic extracts (*C. aurantiifolia)* inhibit the growth of *C.albicans*, as they found that the diameters of the inhibition zones increased with the concentration of the extract, like the anti-bacterial activity.

Table 5: Effect of extract A (Mixed of *Camellia sinensis* and *Citrus aurantifolia*) on the gene expression of virulence genes during the study period for the yeast *C. albicans*

Sample	ΔCTE	ΔCTC	ΔΔCt	Expression Fold Change2^-ΔΔCt
Control	0	0	0	1
CAP1 50	-4.862	-4.174	-0.688	1.611048582
CAP1 75	-4.176	-4.174	-0.002	1.001387256
CAP1 100	-2.864	-4.174	1.31	**0.40332088**
CAP1 200	4.776	-4.174	8.95	**0.002022002**
LIP3 50	-2.316	-1.972	-0.344	1.269270886
LIP3 75	-1.486	-1.972	0.486	0.71400199
LIP3 100	-1.212	-1.972	0.76	**0.590496331**
LIP3 200	-0.748	-1.972	1.224	**0.428094142**
ALS1 50	-0.471	0.36	-0.831	1.778917987
ALS1 75	0.492	0.36	0.132	0.912565489
ALS1 100	1.06	0.36	0.7	**0.615572207**
ALS1 200	4.868	0.36	4.508	**0.043949787**
CAT1 50	-0.997	-1.04	0.043	0.97063447
CAT1 75	-0.741	-1.04	0.299	0.812815602
CAT1 100	-0.796	-1.04	0.244	**0.844400887**
CAT1 200	-0.113	-1.04	0.927	**0.52595089**

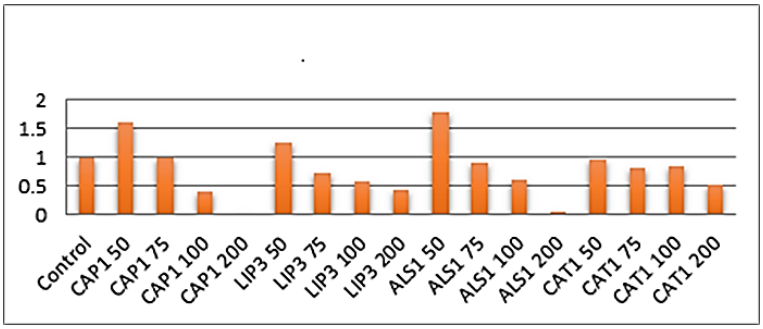

Figure 1: Effect of extract A (Mixed of *Camellia sinensis* and *Citrus aurantifolia*) on the gene expression of virulence genes during the study period for the yeast *C. albicans*

The effects of Mirabilis jalapa extract may be attributed to its disruption of the cell membrane, leading to leakage and cell death; it also appears to inhibit DNA, RNA, protein, and enzyme synthesis [11]. pointed out in their study that the alcoholic

extract of *Mirabilis jalapa* showed an inhibitory effect against *Candida*.

The results in Table 6 and Figure 2 showed that extracts B (Mirabilis jalapa) at 100% and 200% reduced gene expression of virulence factors in Candida yeast, whereas 50% and 75% concentrations had no effect. These results were similar to those of extract A, but when compared with extract A, extract B showed greater reductions in gene expression of virulence factors.

Table 6: Effect of extract B (*Mirabilis jalapa*) on the gene expression of virulence genes during the study period for the yeast *C. albicans*

Sample	ΔCTE	ΔCTC	ΔΔCt	Expression Fold Change2^-ΔΔCt
Control	0	0	0	1
CAP1 50	-6.081	-4.174	-1.907	3.750284386
CAP1 75	-5.164	-4.174	-0.99	1.986184991
CAP1 100	-3.063	-4.174	1.111	**0.462973011**
CAP1 200	-2.252	-4.174	1.922	**0.263888429**
LIP3 50	-6.049	-1.972	-4.077	16.87715707
LIP3 75	-4.825	-1.972	-2.853	7.225012081
LIP3 100	-2.262	-1.972	-0.29	**1.222640278**
LIP3 200	6.228	-1.972	8.2	**0.003400588**
ALS1 50	-3.629	0.36	-3.989	15.87846999
ALS1 75	-2.484	0.36	-2.844	7.180080405
ALS1 100	-1.697	0.36	-2.057	**4.161201066**
ALS1 200	3.69	0.36	3.33	**0.09944206**
CAT1 50	-1.296	-1.04	-0.256	1.194163187
CAT1 75	-1.899	-1.04	-0.859	1.813780658
CAT1 100	-1.339	-1.04	-0.299	**1.230291345**
CAT1 200	11.597	-1.04	12.637	**0.000156994**

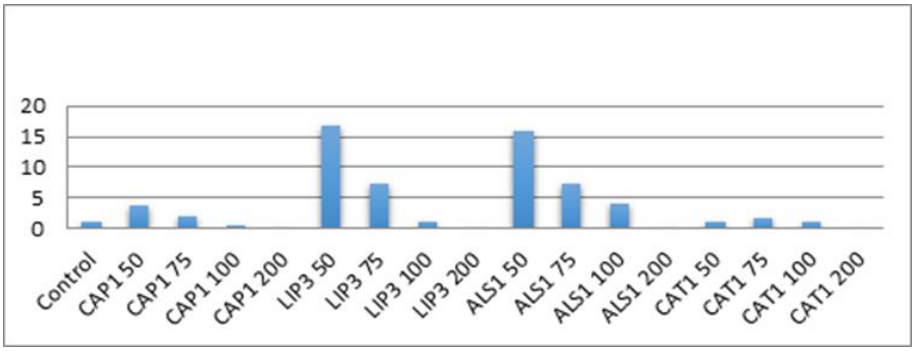

Figure 2: Effect of extract B (*Mirabilis jalapa*) on the gene expression of virulence genes during the study period for the yeast *C. albicans*

Based on what was mentioned above, targeting genes involved in the virulence of pathogens is important in controlling their virulence and thus controlling infection, including the genes in the current study, as the gene (ALS1) is a member of the agglutinin-like ALS sequence of genes that encode surface proteins for *Candida* hyphae and help them adhere to the host endothelial cells and produce biofilms and select host cells [14]. The LIP3 gene encodes the lipase enzyme that degrades fats [19] and is important in biofilm production through its analysis of fatty layers on mucosal tissues and its role in biofilm formation [20]. At the same time, the CAT1 gene encodes catalase, an enzyme important for coping with stress. The oxidative stress that Candida is exposed to (inside the host tissues) by secreting these enzymes as a rapid response in removing the toxicity of free oxygen radicals ROS [21], in addition to the role of the CAP gene in the virulence of the *C. albicans*, represented by the transformation from the yeast form to the filamentous form and its role in the growth of the

filamentous phase and in the level of cyclic adenosine monophosphate (cAMP)[22]. Thus, the results of the current study, represented by a decrease in the expression level (at concentrations of 100% and 200%) of several virulence genes, after treating the pathogens with the solution of the selected plant extracts, are evidence of the efficiency of the extract and its effectiveness as an antifungal and antibiofilm in the studied yeast species.

CONCLUSION

The results of this study, the extract of Mixed *Camellia sinensis* and *Citrus aurantifolia* and extract of *Mirabilis jalapa* have potential as an antifungal agent oral cavity to inhibited growth of oral cavity pathogen, at different concentrations of 50%, 75%, 100%, 200%, the concentrations of 100% and 200% for both extracts gave better results in reducing the level of gene expression of the virulence genes of *Candida albicans*. These plants have no side effects, are safe, and are less expensive than antifungal drugs.

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