

# *Punica granatum* Linn. prevention of oral candidiasis in patients undergoing anticancer treatment

*Punica granatum* Linn. na prevenção da candidíase oral em pacientes que se submetem a tratamento antineoplásico

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## Resumo

**Introdução:** A candidíase oral é considerada uma das complicações da terapia antineoplásica de cabeça e pescoço. Estudos revelam que a fitoterapia vem se mostrando uma alternativa promissora para o tratamento da candidíase. **Objetivo:** Avaliar a efetividade do gel de *Punica granatum* Linn. na prevenção da candidíase oral, em pacientes submetidos à radioterapia associada ou não a quimioterapia para tratamento de carcinoma de células escamosas na região de cabeça e pescoço, e efeitos adversos associados ao seu uso. **Material e método:** Foi realizado um ensaio clínico, duplo cego, no período de 2012 a 2013, com pacientes atendidos em um Hospital de referência para tratamento oncológico. A amostra foi composta por 17 pacientes que não apresentavam os sinais e sintomas de candidíase oral, os quais foram divididos em dois grupos: experimental (n=11): composto por pacientes que utilizaram o gel de *Punica granatum* Linn. 6,25%, desde o início do tratamento antineoplásico e concluído uma semana após o término do esquema terapêutico; controle (n=6): por pacientes que utilizaram o gel de Miconazol 2%, seguindo as mesmas orientações do grupo anterior. Os dados foram tabulados e analisados por meio da estatística descritiva e usado os testes Qui-quadrado e Cálculo da Correção Continuada de Yates (p<0,05). **Resultado:** Não se observou a candidíase oral em 63,6% dos pacientes do grupo experimental, e em nenhum paciente do grupo controle. **Conclusão:** A maioria dos pacientes que fizeram uso do gel experimental não apresentaram os sinais clínicos da infecção fúngica, e não houve a associação de efeitos adversos.

**Descritores:** *Punica granatum*; fitoterapia; radioterapia; *Candida albicans*.

## Abstract

**Introduction:** Oral candidiasis is considered one of the complications of antineoplastic therapy of head and neck. Studies show that herbal medicine has proven to be a promising alternative for the treatment of candidiasis. **Objective:** To evaluate the effectiveness of the gel *Punica granatum* Linn. in the prevention of oral candidiasis in patients undergoing radiotherapy with or without chemotherapy for squamous cell carcinoma of the head and neck, and adverse effects associated with its use. **Material and method:** It was performed a clinical trial, double blind, in the period 2012-2013, with patients seen at a referral hospital for cancer treatment. The sample consisted of 17 patients who did not have signs nor symptoms of oral candidiasis. These patients were divided into two groups: experimental (n=11): composed of patients who used the gel *Punica granatum* Linn. 6.25% since the beginning of the anticancer treatment and completed a week after the end of the treatment regimen; control (n=6): for patients who used the gel Miconazol 2%, following the same guidelines of the previous group. Data were tabulated and analyzed using descriptive statistics, the chi-square test and calculation of continuing Yates correction (p<0.05). **Result:** There was no oral candidiasis in 63.6% of patients in the experimental group and in none of the control group patients. **Conclusion:** Most patients who used the experimental gel showed no clinical signs of fungal infection, and there was no association of adverse effects.

**Descriptors:** *Punica granatum*; phytotherapy; radiotherapy; *Candida albicans*.

## INTRODUCTION

The standard therapy for most of the malign neoplasias in head and neck regions usually consists of surgery or radiotherapy for the treatment of the disease, associated or not to chemotherapy, or they can be concurrent<sup>1</sup>. Both the radiotherapy and the chemotherapy are related to a variety of oral complications, because they do not differentiate neoplastic cells from regular cells, among them, xerostomia, oral mucositis and candidiasis, which can compromise the life quality of the patients during the treatment<sup>2,3</sup>.

Candidiasis is the most common fungal infection of the oral cavity and can present itself in several clinic ways, and the most common is the pseudomembranous candidiasis and the erythematous. The latest presents itself with red spots and burning sensation and the previous one with white, creamy, detachable plates and with bad breath<sup>4-6</sup>.

The irradiated patients have a higher trend to develop oral infections caused by fungi and bacteria<sup>7</sup>. The increased risk of oral candidiasis is probably caused by the fall of salivary flow as a consequence of radiotherapy. Besides, a possible explanation for irradiated patients' greater disposition to candidiasis, is a reduced phagocytic activity of the salivary granulocytes against these microorganisms<sup>8</sup>.

Despite the existence of several antifungal agents of topical and systemic use for the treatment of candidiasis, the increasing resistance of the infecting agents to allopathic medicines, besides the adverse and side effects related to the existing drugs, has motivated researchers to seek for new treatment options, and the phytotherapy is one of them<sup>6</sup>. Products from plant origin have been studied a lot due to their low toxicity related to their use in the traditional medicine<sup>9</sup>.

Pomegranate, *Punica Granatum* Linn., is one of the medicinal plants that presents antifungal activity. It is chemically composed by tannins (polyphenolic substances) and alkaloids that are substances supplying antimicrobial activity. For being rich in phenolic compounds such as tannins, Anthocyanins, flavonoids, among other components that have got antioxidant properties, its anti-carcinogenic, anti-inflammatory and antimicrobial potential has been related to these active agents present in different parts of the plant<sup>10,11</sup>.

Based on the above considerations, the present study has as objective to evaluate the effectiveness of the gel *Punica granatum* Linn. at the prevention of oral candidiasis, in patients submitted to radiotherapy associated or not to chemotherapy, for the treatment of squamous cells carcinoma in the head and neck region, as well as to verify the occurrence of adverse effects associated to the use of the medicine.

## MATERIAL AND METHOD

This is a double-blind, perspective, longitudinal, clinical trial with direct and indirect observation technique, by means of a suitable clinical exam. It was performed between 2012 and 2013, with patients seen at Hospital Dr. Napoleão Laureano, located in Paraíba state. The research started after the approval by the

Ethics and Research Committee of Paraíba State University under register CAAE 0006.0.133.000-12, and according to the national and international guidelines and regulated by the Declaration of Helsinki.

The sample consisted of 17 patients from both genders, older than 18 years old, for the first time submitted to external radiotherapy for the treatment of malign neoplasias in head and neck regions, with exclusive indication or concurrent with chemotherapy or surgery and whose radiation field, covered at least half the mucosa coating area of the oral cavity.

Patients who used other antifungal medications, used incorrectly the indicated medication, did not follow the protocol suggested by the researchers and the ones with Karnofsky Performance Status (KPS) lower than 70 were excluded from the research, in other words, unable to perform regular activities, requiring special care.

At the first appointment, it was performed lab exam for fungus research, in order to confirm the absence of oral candidiasis clinical signs and symptoms. Next, the patients were divided in two groups. Group 1 (n=11) used *Punica granatum* L. gel 6.25%, as oral candidiasis prevention. These patients started using the gel as a preventive way at the beginning of the radiotherapy fractioning protocol associated or not to chemotherapy and concluded one week later after the ending of radiotherapy scheme, with frequency of four times a day, half an hour later the oral hygiene. Group 2 (n=6) used Miconazol gel 2%, as oral candidiasis prevention, following the same protocol as the previous group.

The hydro alcoholic extract of the fruit skin of *Punica granatum* Linn. (pomegranate) used in this research, was acquired from the company All Chemistry do Brasil Ltda<sup>®</sup>. After obtained the extract, *Punica granatum* L. gel was elaborated at the concentration of 6.25%, based on the studies of Vasconcelos et al.<sup>12</sup> and Vasconcelos et al.<sup>13</sup> who verified *in vitro* and *in vivo* its antimicrobial potential in face of *S. mutans*, *S. mitis* and *C. albicans*, in concentrations that vary from 1:1 to 1:1024. The non-toxicity of this gel corresponded to ¼ below DL<sub>50</sub>.

The therapeutic and clinic effectiveness of the drugs was evaluated through intraoral physical exam. The patients were weekly evaluated during all the antineoplastic treatment. If they presented clinic signals and/or symptoms of oral candidiasis, they were submitted to more specific laboratory examination - culture, for the identification of the type of fungus. In face of a positive result, these patients no longer participated in the research and the hospital protocol was introduced for oral candidiasis treatment. The collection of the first material of the oral cavity was performed at the dorsal surface of the tongue, that according to Neville et al.<sup>2</sup> is one of the oral places more attacked by the infection.

## RESULT

Most of the patients was of male sex (82.4%), with average age of 60.7 years (DP=11.1), varying from 38 to 77 years old, presenting ethnicities: white (23.5%), black (11.8%) and brown (64.7%). The tumor location more prevalent was in the oropharynx (35.2%), followed by the tongue (29.4%). The smoking and alcoholism habits were predominantly present in both groups,

according to Table 1. The use of dental prosthesis was verified in 35.3% of the patients, among them 66.6% used total prosthesis and 33.3% partial prosthesis.

Most of the patients had as histopathological diagnosis, moderately differentiated squamous cell carcinoma, being 35.3% in group 1 and 23.5% in group 2. The most prevailing suggested treatment was chemotherapy associated to radiotherapy, corresponding in

group 1 to 4.2% and in group 2 to 35.3% with fractioning scheme of 1.8 Gy for the majority.

According to chi-square tests and Yates continued correction calculation, in group 1 oral candidiasis did not appear in 63.6% of the patients, while in group 2 no patient developed candidiasis, being adopted a confidence interval of 95% and significance level of 5% ( $p < 0.05$ ) (Table 2).

**Table 1.** Habits evaluation and general patient conditions according to the groups, Campina Grande/PB, Brazil, 2015

Variables	Answers	Group 1		Group 2	
		F	%	f	%
Smoking	Yes	10	90.9	6	100
	No	1	9.1	0	0.0
Alcoholism	Yes	7	63.63	6	100
	No	4	36.37	0	0.0
Presents comorbidity	Yes	7	63.63	2	33.33
	No	4	36.37	4	66.67
Type of comorbidity	Absence	4	36.37	4	66.67
	Asthma	0	0.0	1	16.66
	Diabetes	1	9.1	0	0.0
	Hypertension (THERE IS)	5	45.45	1	16.66
	THERE IS/ Diabetes	1	9.1	0	0.0
KPS	70.0	3	27.27	2	33.33
	80.0	6	54.55	4	66.67
	90.0	2	18.18	0	0.0
Brushing frequency	Twice	5	45.45	2	33.33
	Three times	5	45.45	3	50.01
	More than three times	1	9.1	1	16.66

**Table 2.** Evaluation of mucositis, dysgeusia, candidosis and xerostomia appearance during the treatment according to the groups, Campina Grande/PB, Brazil, 2015

Variables	Answers	Group 1		Group 2	
		f	%	f	%
Mucositis	Appeared	8	72.7	3	50
	Did not appear	3	27.3	3	50
	$\chi^2$ (p)	0.16 (0.68)			
Dysgeusia	Appeared	7	63.6	4	66.7
	Did not appear	4	36.4	2	33.3
	$\chi^2$ (p)	0.00 (1.00)			
Oral Candidiasis	Appeared	4	36.4	0	0.0
	Did not appear	7	63.6	6	100
	$\chi^2$ (p)	1.19 (0.27)			
Xerostomia	Appeared	6	54.5	4	66.7
	Did not appear	5	45.5	2	33.3
	$\chi^2$ (p)	0.00 (1.00)			

## DISCUSSION

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There is some correlation between cancer treatments and the appearance of oral lesions. The magnitude of these effects depends on a series of factors related to the treatment, tumor and patient<sup>14,15</sup>. The correct understanding of these signs and their correlation with symptoms and drugs or radiation used in cancer treatments turn these types of manifestations more predictable, what can facilitate the prevention and the treatment of these alterations, being of great importance the integration of Odontology with the medical oncology team.

In this study it was observed that the majority of the samples corresponded to the male gender, supported by several authors<sup>2,14,16,17</sup>. Regarding the age range, the patients' average age was 60.7 years, similar results were reported by Alvarenga et al.<sup>17</sup> and Deng et al.<sup>14</sup>. Moreover, adopting the Geography and Statistics Brazilian Institute classification, there was predominance of brown-skinned, disagreeing from Alvarenga et al.<sup>17</sup> who verified that approximately 90% of the patients with head and neck cancer were white-skinned and in line with Gervásio et al.<sup>18</sup>, where there was predominance of black (33.5%) However, such discrepancies can be explained by the location where the studies were performed, by the prevalence of each race in different regions of the country.

Despite the oral cancer etiology being multifactorial and occur in several phases, smoking and alcoholism are considered the main risk factors. Depending on the type of smoke and alcoholic drink, as well as, the habit frequency and duration, this risk is increased when there is association of these two factors<sup>1,2,19</sup>. Alcohol increases the permeability of the oral mucosa cells to the carcinogenic agents, besides presenting carcinogenic substances produced by ethanol metabolites, increasing by 30 times the probability of developing oral cancer<sup>19</sup>. In this study, most of the patients were smokers and alcoholics, what reinforces the association between these two factors and the development of oral cancer.

Oral candidiasis is a very common infection in patients irradiated in the head and neck region. However, in this research, it has not showed up in most patients and when present, it varied in the weeks during the radiotherapy, being pseudomembranous candidiasis the most prevailing clinical form. This data is aligned with the findings of Jham, Freire<sup>7</sup>. These patients are more likely to develop oral infections as a consequence of the immunosuppression, due to the falling of salivary flow, deficient oral hygiene, among other factors, such as age and mucositis presence<sup>20</sup>. The absence of candidiasis in most patients of this research can be possibly related to the effectiveness of the gels as a preventive agent of the fungal infection. Oral hygiene instructions were also weekly transmitted to patients, such as brushing technique and neutral toothpaste use, what can have influenced in the reduction of fungal oral infection occurrence.

Lalla et al.<sup>21</sup> verified the prevalence of clinic fungal infection of 7.5% at the pretreatment, 39.1% during the treatment and 32.6% after the end of the radiotherapeutic treatment. However, among those who were submitted to both radiotherapy and chemotherapy, the prevalence of oral colonization with fungal organisms was of 48.2% before the treatment, 72.2% during the treatment, and 70.1% after

the treatment, data similar to the findings of Deng et al.<sup>14</sup>. In the present study, the fungal infection appeared in 36.4% patients of group 1, however, it was impossible to categorize in which week it was most prevailing due to the heterogeneity of candidiasis appearance, associated to a reduced group of individuals, so that we cannot claim in which week the patients would be more attacked by oral infection, when submitted to radiotherapy or chemotherapy treatment.

In this study, both groups used therapeutic protocols with preventive function, among them the *Punica granatum* L. gel that has already had its action over fungal microorganisms confirmed by the action of the tannins through its astringent property and other not very much clarified mechanisms<sup>11,12</sup>. Among the hypothesis over the antimicrobial action mechanisms of these phytochemicals, include enzyme inhibition, cell metabolism modification by the action over membranes and the complexing metal ions with consequent decrease of its availability for the microorganisms metabolism<sup>22</sup>. *In vitro* study<sup>23</sup> identified, through scanning and transmission electron microscopy, that the yeasts have their morphology altered when exposed to the action of crude extract or of ellagitannins isolated from the skin of the fruit *Punica granatum*, presenting a thick cell wall, alterations in the space between the cell wall and the plasmatic membrane, vacuoles and a reduction of the cytoplasmic content.

Several *in vitro* studies, performed with extracts obtained from different parts of the *P. granatum*, proved their antifungal activity<sup>9,23-26</sup>. However, only one clinic study with humans<sup>12</sup> verified the therapeutic potential of the gel *Punica granatum* at 10%. The results show inhibitory activity on the adhesion of different bacteria and yeast strains commonly found in the oral cavity. This way, gel *Punica granatum* Linn can be used to control the bacteria and yeasts responsible for oral infections, such as cavities, periodontal diseases and candidiasis.

Despite several medications are used at the prevention and treatment of oral candidiasis, among them nystatin and miconazole<sup>4,20,21</sup> it still does not exist an efficient phytotherapeutic method or agent, of routine use, with less adverse effects, such as, dermatitis, nausea, vomit, itching and irritation<sup>20,21</sup>, in order to prevent or treat oral fungal infection.

Based on the above, there is the need of more studies, like this, which can evaluate *in vivo* the use of phytotherapeutic products, such as the pomegranate, for the prevention and control of oral alterations. Among these, candidiasis, resulting from antineoplastic treatments, such as radiotherapy and chemotherapy, and this way provide a better life quality to patients with cancer, once most of the researches that involve pomegranate as antifungal agent are "*in vitro*"<sup>9,10,13,23</sup>.

## CONCLUSION

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Most of the patients who used *Punica granatum* L. gel did not present clinical signs of fungal infection. Besides there was no association of adverse effects.

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## CONFLICTS OF INTERESTS

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The authors declare no conflicts of interest.

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Received: October 9, 2015

Accepted: August 25, 2016