

**Title: Synergistic effect of Beta-caryophyllene alone and in combination with ketoconazole against *Trichophyton rubrum* strains**

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**Abstract:**

**Introduction.** *Trichophyton rubrum* is a dermatophytes fungi, fungal pathogen responsible for dermatophytosis, clinical skin infections prevalent in tropical regions due to the temperature and humidity of the tropical climate propitiate an ideal habitat for its spread. Natural products are essential in the discovery of new drugs.  $\beta$ -caryophyllene is a secondary metabolite found in many essential oils. This bicyclic sesquiterpene has been commonly used as a fragrance and flavouring agent in citrus flavors, soaps, detergents, and also in a variety of beverages and food products. The antifungal and antibacterial activities have been reported for several microorganism strains. This study aimed to investigate the synergistic effect between  $\beta$ -caryophyllene and ketoconazole against *T. rubrum* strains.

**Materials and methods.** All chemicals were obtained from Sigma–Aldrich Co (St. Louis, MO, USA), at the highest available grades. A total of 4 strains of *T. rubrum*, were included in this study. The assay was performed in accordance to guidelines of Clinical and Laboratory Standards Institute. The modulatory activity assays were performed to determine the combined effect of the  $\beta$ -caryophyllene with the ketoconazole, standard antifungal drug, against strains of *T. rubrum* by the checkerboard technique. The interaction of the drugs was ascertained by calculating the fractional inhibitory concentration index.

**Results.**  $\beta$ -caryophyllene demonstrated capacity of synergistic activity against all *T. rubrum* strains, especially for the *T. rubrum* LABMIC 0103 and *T. rubrum* LABMIC 0104, whose FICI value were 0.25 and 0.26, respectively. The FICI value for the strains *T. rubrum* LABMIC 0113 and *T. rubrum* LABMIC 0102 were 0.5. These results obtained showed a capacity of modulatory antifungal activity when it was combined  $\beta$ -caryophyllene with ketoconazole on the growth inhibition of dermatophytes.

**Conclusions.** These results indicated a modulatory activity between  $\beta$ -caryophyllene and ketoconazole against dermatophytes strains and corroborate with previous studies that demonstrate antifungal activity against *T. rubrum* strains. Synergism studies represent an alternative to the control of infectious diseases, especially caused by multidrug-resistant microorganisms strains.

**Keywords:** bicyclic sesquiterpene, dermatophytes, essential oil, modulatory effect.