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Antioxidant adaptation by eugenol and its derivatives and their affect on the expression of virulence in *Candida* species

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Present work investigates the antifungal activity and mode of action of eugenol (EUG), and its three derivatives - methyl eugenol (MEUG), eugenyl acetate, myresticin, thymol (THY) and carvacrol (CARV). EUG and its derivatives were tested for antifungal activity by standard methods of CLSI. The mean MIC of EUG was 500 mgL^{-1} which reduced down to 350, 100 1 and 50 mgL^{-1} with MEUG, THY and CARV respectively. EUG and its derivatives varied in their mechanism of action depending upon the period of exposure. Short exposures of 5-15 minutes resulted in reduced H^+ efflux by the H^+-pump. An exposure of 1h resulted in membrane leakage while prolonged exposures of 18 h resulted in highly reduced ergosterol content indicating the involvement of ergosterol biosynthesis pathway in mechanism of action of test compounds. It was also observed that exposures of 8 h, at very low concentrations induce oxidative stress in yeast contributing to further membrane disintegration. From our studies we conclude that EUG and its derivatives induce production of free radicals which stimulates the enzyme SOD. An increased SOD activity resulted in an increase in the concentration of H_2O_2 which further stimulates the peroxide eliminating enzyme, primarily GPx. It is noteworthy that the levels of GSH an essential substrate of GPx were drastically reduced by the test compounds and this reduction gets even greater as increased levels of H_2O_2 decrease the activity of G6PDH which provides reducing equivalents to GR, an enzyme that recycles GSH from GSSG. As a result, decreased G6PDH activity aids further in the reduction of GSH. Again, reduced availability of GSH explains decreased GPx activity. Another enzyme characterized to eliminate H2O2 is catalase, which triggers a cellular response leading to an increase in its activity. Hence increase in the activity of two important antioxidant enzymes SOD and catalase, clearly demonstrates an increase in the concentration of ROS when the *Candida cell* were exposed to the EUG and derivatives. However, these enzymatic responses were not enough to defend the cell completely against such a high rise in ROS and therefore did not meet the required cellular antioxidant demand. Ultimately, the outburst of free radical production led to severe lipid peroxidation. Cell death on exposure to EUG and its derivatives hence may be due to (i) decrease in the rate of H^+ efflux (ii) reduced ergosterol content (iii) Induction of oxidative stress in the cell (iv) These processes impair membrane structure and function and as a result form lesions. Infection process of *C. albicans* is characterized by crucial pathogenicity markers. The initial process of germ tube induction followed by the secretion of hydrolytic enzymes help in the invasion of the host cells. EUG and its derivatives significantly inhibited these pathogenicity markers even at sub-MIC values. The expression profile of selected genes associated with *Candida* virulence by RT-PCR showed a reduced expression of *HWP1, SAP1* and *PLB2* genes in *C. albicans* cells treated with eugenol and its derivatives. Virulence traits depend upon the cells antioxidant status which was impaired by the test compounds. Further studies using animal models are necessary to see the *in vivo* efficacy of the compounds.

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