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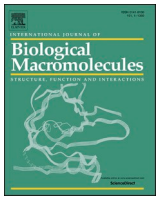

Methyl 4-pyridyl ketone thiosemicarbazone (4-PT) as an effective and safe inhibitor of mushroom tyrosinase and antibrowning agent

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ABSTRACT

Enzymatic browning is of concern as it can affect food safety and quality. In this study, an effective and safe tyrosinase inhibitor and anti-browning agent, methyl 4-pyridyl ketone thiosemicarbazone (4-PT), was synthesised and characterised using Fourier-transform infrared (FTIR) spectroscopy, CHNS elemental analysis, and proton (^{1}H) and carbon-13 (^{13}C) nuclear magnetic resonance (NMR) spectroscopy. The vibrational frequencies of 4-PT were studied theoretically using vibrational energy distribution analysis (VEDA). Density functional theory (DFT) was applied to elucidate its chemical properties, including the Mulliken atomic charges, molecular electrostatic potential (MEP), quantum theory of atoms in molecules (QTAIM) and reduced density gradient non-covalent interactions (RDG-NCIs). Moreover, 4-PT was compared with kojic acid in terms of its effectiveness as a tyrosinase inhibitor and anti-browning agent. The toxicity and physicochemical properties of 4-PT were predicted via ADME evaluation, which proved that 4-PT is safer than kojic acid. Experimentally, 4-PT (IC50 = 5.82 μM, browning index (10 days) = 0.292 ± 0.002) was proven to be an effective tyrosinase inhibitor and anti-browning agent compared to kojic acid (IC50 = 128.17 μM, browning index (10 days) = 0.332 ± 0.002). Furthermore, kinetic analyses indicated that the type of tyrosinase inhibition is a mixed inhibition, with K_m and V_{max} values of 0.85 mM and 2.78 E-09 μM/s, respectively. Finally, the mechanism of 4-PT for tyrosinase inhibition was proven by 1D, second derivative and 2D IR spectroscopy, molecular docking and molecular dynamic simulation approaches.

1. Introduction

Foods comprise complex constituents, such as nutrients and bioactive compounds, each with their own functions. Food spoilage, such as food browning in fruits and vegetables, involves undesirable food phenomena caused by enzymatic browning reactions that physically and chemically modify complex food matrices [1]. Enzymatic browning is a major contributor to the loss of quality in foods and beverages; this has a significant impact on the sensory and nutritional properties of food products, such as their colour, taste, and flavour, and subsequently reduces their shelf life [2]. The main enzyme responsible for the enzymatic browning reaction is the copper-containing polyphenol oxidase (PPO), a tyrosinase enzyme present in food.

Copper-containing PPO plays a huge role in enzymatic browning. Tyrosinase (EC 1.14.18.1) is a metalloenzyme that is responsible for the formation of melanin. When mechanical and physical factors lead to tissue damage, the PPO in food initiates the oxidation of polyphenols into their corresponding quinones, which then undergo polymerisation with other quinones or phenolics to produce melanin, resulting in brown pigmentation [3]. Effective and safe tyrosinase inhibitors are used to prevent such pigmentation to enhance the shelf life and quality of food products and, thereby, improve their market value. Therefore, the development of tyrosinase inhibitors can benefit many industries, such as the cosmetic and medicinal industries and, most notably, the food

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