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Novel pyrimidine derivatives and black cumin as xanthine oxidase inhibitors: synthesis, docking study and formulation

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Abstract: The enzyme xanthine oxidase is crucial to the development of hyperuricemia and gout owing to the fact that it acts as a catalyst for the oxidation reaction that turns hypoxanthine and xanthine into uric acid. In this work, to attempt discovery of novel xanthine oxidase (XO) inhibitors, we developed a method for optimizing the Nigella sativa oil extraction by considering the seed size particles, the liquid seed ratio, the duration of the extraction procedure and the temperature of extraction. On the other hand, new pyrimidine and triazolopyrimidine derivatives were prepared in an attempt to mimic the pyrazolpyrimidine structure of allopurinol (a well-known xanthine oxidase inhibitor drug). A series of thiouracils 4a-c, hydrazinopyrimidines 5a-c and triazolopyrimidines 6a-c were designed and synthesized. The *in vitro* enzymatic assay was used for assessing the natural and synthesized substances for how effectively they inhibit xanthine oxidase. Most of the developed compounds were shown to have strong xanthine oxidase inhibitory activities, while Nigella sative extract and compound 6b ranked as the most effective inhibitors (IC_{50}=1.87 and 0.63µg/ml, respectively, versus Allupurinol's IC_{50}=0.62µg/ml). Nigella sative extract and compound 6b showed potent activity (IC_{50}=0.60µg/ml). In addition, compound 6b was formulated as effervescent granules and exhibited good flow-ability properties. To further understand the approach of binding between synthesized compounds 6a-c and xanthine oxidase, a molecular docking investigation was conducted. These findings highlight the discovery of a novel group of xanthine oxidase inhibitors with the potential to improve the state-of-the-art treatment for gout.

Keywords: Black seed, pyrimidine and triazolopyrimidines, xanthine oxidase inhibitors, effervescent granules, Docking Study.