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Elucidation of molecular mechanisms of activity of *Echinacea spp.* constituents for possible treatment of COVID 19 by computer-aided methods

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Echinacea spp. have long history of use, dating from American natives. Among ten, three species (*Echinacea purpurea (L.), Echinacea pallida (Nutt.)* and *Echinacea angustifolia (DC.)*), are the most used, alone or in mixes, for treatment of various conditions, such are infections, cancers etc. Recently, it was shown that *Echinacea spp.* are effective in treatment of COVID 19, inhibiting progress of SARS CoV2 development. Due to availability of structures of certain number of chemical constituents of *Echinacea spp.* and 3D structures of possible targets included in processes of interaction, elucidation of its molecular mechanisms of action was performed by computational methods.

Three approaches for evaluation of molecular mechanisms of *Echinacea spp.* constituents (24 from *Echinacea purpurea* and 10 from other *Echinacea spp.*) for possible treatment of recent COVID 19 pandemia are presented. First, docking studies of *Echinacea spp.* constituents (34) were performed on three targets, according to literature as the most important for SARS CoV2 virus spread and development: SARS CoV2 spike protein and angiotensin converting enzyme (ACE2) receptor responsible for virus entry, as well as SARS-CoV-2 metalloproteinase M^{pro} as the most responsible in mediation of viral transcription and replication. Second, physicochemical properties and pharmacokinetic-related characterization (Lipinksi Rule of five) of *Echinacea spp*. constituents in conformation with minimum energy, were performed by Data Warrior program. Results show that 4/34 compounds have negative values of log P (hydrophilic), 6/34 showed negative results regarding selection by Rule of five, among which 5 significantly differ in H-bonding capacity, which indicates different properties for oral absorption and distribution within the organism, as well as mode of action. Drug likeness, calculated for fragments of 34 constituents, is scattered within 15 units of difference. Third, the probability of interaction of *Echinacea spp.* constituents with targets was estimated by use of SwissTarget Prediction program, based on query molecule showing activity on certain class of targets. Results showed that cannabinoid receptors (CNR) 1 and 2 (17 and 16 units) and peroxisome proliferatoractivated receptor gamma (PPARγ) (15 units) are the most preferable targets for interactions. Possible molecular mechanisms involved in evidented pharmacological records in treatment of COVID 19 by *Ehinacea spp.* were elucidated with regard of results of all three methods.