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REVIEW

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Computer-Based Tools for Structural Characterizations and Activity Specifications of Natural Products: A Quick Review

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ABSTRACT. Natural products have been always known for their benefits for supplying food and drug for human kind survival for whole history. Using original forms of such compounds or their essential substances could provide several types of applications. Besides highlighted benefits, several limitations prevent such substances to work properly for people of all around the world. Therefore, carful examining their structural characterizations and activity specifications could help to provide specified functions or to propose new related derivatives. Computer-based tools are among useful tools for achieving such purposes, in which the model systems could be investigated at the lowest molecular and atomic scales. Such works provide *in silico* media for investigating various features of structures and their related functions. As a consequence, further developments of natural products for specified purposes could be led by the means of computer-based tools.

KEYWORDS. Natural product; Computer; *In silico*; Molecular modeling; Computational analysis.

INTRODUCTION. Natural products have been always using by human kind for different purposes such as food and drug for many years.[1] Such compounds derived from natural resources have been used originally or their essential substances have been extracted for further purposes and applications.[2] Curcumin as an example, which is known very well from the souvenirs of regions of eastern Asia, is one of the major natural products with verities of applications from additive to anticancer.[3-5] Another example is stevia with sugar taste very much helpful for those of diabetic patients besides its important role in beverage industries.[6-9] Therefore, it could be seen that natural products have significant roles in humankind life, in which they should be still characterized for specified applications.[10] So many methodologies have been developed for investigating the characteristic features of such compounds with almost unknown points.[11] Based on experiments, extraction methods of essential substances have been developed and the techniques for characterizing substances fractions have been used for determining what are inside such natural compounds.[12] Besides the original substances of natural resources, their synthetic analogous and derivatives have been developed for specified purposes and applications for using under controlled dosage and material.[13] Although these materials are nature friendly, but it is still really unknown how much toxic they are.[14] Therefore, they should be used under control to have benefits for health avoiding harmful effects.[15] Moreover, the geographical availability of natural products all around the world is another major

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limitation for using such natural based compounds for people of different places.[16] Therefore, it is indeed a must to work on classification and characterization of natural products for developing their applications as much as possible.[17] To this point, two computer-based methodologies were specified here for performing investigations on natural products related materials. It is important to note that the computer-based methodologies could provide *in silico* media for investigating materials at the molecular and atomic scales using computer hardware facilities, software programs and theoretical backgrounds in addition to molecular models.[18-22] Such *in silico* media could help the researchers to isolate the chemical substances to work on their characterizations and specifications at the lowest scales even subatomic units.[23] To achieve the purpose, structural characterizations and activity specifications could be done for chemical substances to introduce them for further applications regarding the already expected purposes or generating new advantages.[24] Earlier works indicated advantages of computer-based approaches for exploring various features of natural products parallel or prior to experiments, in vitro or in vivo analyses.[25-30] Therefore, two specified computer-based approaches of structural characterization and activity specification were described here for pushing forward the research attempts of these fields.

STRUCTURAL CHARACTERIZATION. In spite of types of chemical substances, the structures are very much important to determine the predicted or expected activity of related material. Structure-activity relationship (SAR) is an important concept showing the importance of structure for determining the corresponding activity.[31] Despite the atomic component of a molecule, the geometrical positions and orientations are very much important for determining their features.[32] In contrast with the closed chemical formula indicating only the types and numbers of atoms, such as H_2O, their open structural formula could provide insightful information about the investigated molecules. Indeed, geometrical positions and orientations could yield different energies and stabilities for the structures, in which both of them are very much dominant for determining reactivity level of a molecular system.[32] Moreover, movements of only hydrogen atoms in so many of biological and natural product could yield tautomers with significant deviations in properties and features.[33] Therefore, employing an approach to systematically investigate such structural characterization could help to go further inside the mystery of natural product systems to characterize new features or to propose new derivatives. To this aim, computational chemistry provided several types of methodologies regarding the structural characterizations of matters at the lowest molecular and atomic scales even subatomic units.[34] Density functional theory (DFT) is a very much useful approach for investigating materials as much precise as possible by examining the subatomic units features and characters.[35] DFT calculations could be regularly performed on small molecular systems with few numbers of atoms, but recent methods have been developed for performing calculations on larger models even complicated systems.[36] By doing such DFT calculations, the energy of structures could be determined regarding the geometrical positions and orientations, in which the energy values will be changed upon changing such geometrical features. Therefore, stabilities of different conformations of structures could be very well detected for this purpose. Geometrical optimization processes and molecular and atomic descriptors evaluations could be all done through DFT calculations.[37] For this purpose, software programs such as GAMESS, Gaussian and ORCA are useful for performing calculations.[38-40] Graphical visualizers such as ChemCraft, Avogadro and Gaussview could help to provide visual representations of calculated results for atomic and molecular systems.[41-43] Web-based databases such as ChemSpider could provide 3D structures of almost all chemical substances to be included as input files in the calculations.[44] As a consequence, choosing a proper theoretical method, using a software and a good computer and designing the initial 3D structure models could all help to provide *in silico* media for solving a problem at the molecular and atomic scales. For natural products with known essential substances, such computer-based works could help to propose derivatives with specified chemical and physical properties. An example work has been already done for chemical analysis of glucose amine as the main component of chitosan to see the effects of structural

modifications on the initial properties.[45] Another example work has been done for curcumin with structural combinations modifications to see the capability of such natural product for drug delivery purpose (Fig. 1).[46] It could be seen that several problems could be solved through *in silico* media but with initiating a proper setup specified for each structural system.

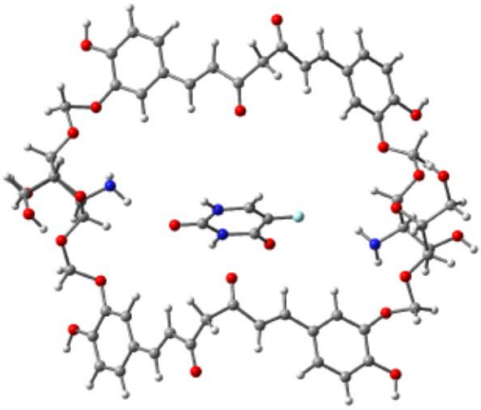

Fig. 1: Complex model of FU–Chit2–Cur2.[46]

ACTIVITY SPECIFICATION. When calling activity, it implies for function of a chemical substance in biological media especially towards enzyme targets in the aspects of drug design and discovery.[47] For natural products, such medical applications have been always at the first rank of attentions regarding developing them for specified applications for living systems survival.[48] Within performing computer-based works, structural features could be evaluated and their functions could be examined. In this regards, contents of previous section showed the importance of performing DFT calculations for achieving optimized structures and corresponding features. In this section, molecular docking (MD) simulation approach would be described as a useful tool for showing activity specifications of natural products.[49] Such MD tool requires 3D structures of micro and macro molecules named ligand and target respectively to investigate interactions of these counterparts in computer systems. Again in previous section, it was described how to find 3D structures of small molecules of ligands and how to reach to their optimized stability levels. For macro molecule targets, 3D structures could be found from protein data bank (PDB) web-based database.[51] Since the conformational changes of micro molecules are always more than those of macro molecules, such target structures could be fixed unchanged during performing MD simulation. AutoDock and SwissDock are two local and online tools respectively for performing MD simulations of ligand-target complex formations.[51, 52] In both of the mentioned tools, the best conformation of ligand towards the target could be identified to show the activity of ligand regarding energy quantities and interaction qualities. PyMol and Discovery Studio could be also used for visualizers of the model systems of MD simulations.[53, 54] Earlier works indicated advantages of such MD simulations to show medicinal applications of curcumin in different aspects.[55, 56] Another example showed such advantage for examining function of steviol in biological systems (Fig. 2).[57, 58] As a consequence, such ligand-target complex formations could yield to examining activity specifications for natural product for different purposes.

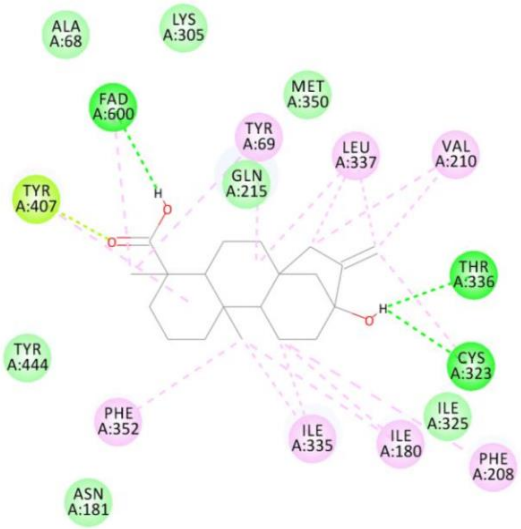

Fig. 2: Steviol…MAO-A interacting complex.[58]

CONCLUSION. In this quick review article, useful computer-based tools were described for investigating structural characterizations and activity specifications for natural products related substances. Performing DFT calculations was proposed for doing structural characterizations whereas perfuming MD simulations was proposed for doing activity specifications for natural products. For both mentioned aspects, existence of 3D structures and carful initiation of computational setup were important to obtain reliable results. In this regard, visualizers could help to represent the results in visual modes to show what has happening inside the chemical structures of natural products and their functions in living systems. By formation of ligand-target complexes, activity of

natural product could be specified regarding expectations on their roles for medication of human kind for long history. As a consequence, employing computer-based tool could provide *in silico* media to carefully examine natural products related structures and their functions for developing their applications or proposing new related derivatives.

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