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The Exploration of Medicinal Plants' Phytochemical Compounds as Potential Inhibitor Against Human α-3 Nicotinic Acetylcholine Receptors: The Insight from Computational Study

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Abstract. Recent trends in health care demonstrate the significant use of herbs as preventive or therapeutic agents against multiple types of diseases, including respiratory disorder caused by cigarette smoking. Thus, in this present study, we explored the potential of medicinal plants' phytochemical compounds as an inhibitor against the human α-3 nicotinic acetylcholine receptor (NAchR). The computation prediction was performed to evaluate the energy and possible interactions among the ligands and target protein. Specifically, the 2D structure of bioactive compounds was retrieved from PubChem database. On the other hand, the protein sequences of human α-3 NAchR were obtained from Uniprot and protein database. The 3D structure was then built up through SWISS-MODEL. Additionally, protein and ligand preparation was employed to optimize the molecular interaction results. The final step of this screening through molecular docking approach was performed using data visualization and analysis. In this study, we found that there are three potential compounds as an inhibitor against α-3 NAchR based on their energy-free binding, namely, Theaflavin-3-Gallate, Asiaticoside, and Theaflavin-3,3-Digallate. Therefore, work indicates that the medicinal plants' bioactive compounds might be the potential to develop as inhibitory agents for α-3 NAchR to minimize the negative effect of nicotine.

INTRODUCTION

Cigarette consumption has been dramatically increased over the years. Statistical data informed that approximately ten million cigarettes are actively traded each minute. Several studies also have demonstrated that cigarettes contain dangerous and toxic chemicals, one of which is nicotine [1]. Ironically, the use of tobacco, causing more than five million deaths per year in both active and passive cigarette smokers. Recent facts also showed that smoking cigarettes could cause several new cases or increase the incidence of diseases such as cancers, respiratory diseases, cardiovascular diseases, and reproductive disorders [2].

Multiple therapeutic modalities have been proposed. A recent strategy to minimize the adverse effect of cigarette smoking is by targeting and inducing the aryl hydrocarbon receptor (AHR)-repressor, which, in turn, mediates the expression of anti-inflammation rate [3]. However, this approach needs more improvement to optimize the treatment results [3,4]. Genetic profiling study demonstrated that the NAchRs gene is expressed in inflamed lung diseases such as chronic obstructive pulmonary disease (COPD) of patients. From a molecular perspective, nicotine can bind to the NAchRs protein, which in turn, induces several biological signaling and activation, including inflammation [5,6]. Therefore, targeting NAchRs may be the potential to reduce the adverse effect of cigarette smoke.

On the other hand, the recent trend showed the increasing use of indigenous plants as the new alternative to overcome several types of diseases [7,8]. Despite their fewer side effects, traditional medicine also offers several advantages in terms of availability and economic perspective. Numerous traditional herbs have been used as therapeutic purposes in tribal communities such as *Camelia sinensis* (black tea), *Cantella asitica* (cantella),

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Orthosipon aristatus (cat whiskers), *Moringa oleifera* (moringa), and *Kaempferia pandurata* (fingerroot). Ironically, the scientific reports of these medicinal plants are based on minimal data. Therefore, in this study, we explored the potency of bioactive compounds from *Camelia sinensis*, *Cantella asitica*, *Orthosipon aristatus*, *Moringa oleifera*, and *Kaempferia pandurata* as inhibitor for the α-3 NAchR to minimize and reduce the adverse effect of nicotine.

EXPERIMENTAL DETAILS

Several plants' bioactive compounds from indigenous were assessed to evaluate the possible molecular interaction with α-3 NAchR, including *Camelia sinensis* (Theaflavin-3-Gallate, Theaflavin-3,3-Digallate, Theaflavin, and (-)-Epicatechin-Gallate) [9], *Moringa oleifera* (Ellagic acid, Quercetin, Glucosinolates, and Kaempferol) [10-12], *Cantela asitica* (Asiaticoside), *Orthosipon aristatus* (Orthosiphol B), and *Kaempferia pandurata* (Panduratin A and Hydroxypanduratin A) [13]. Molecular interaction prediction among ligands and target protein was performed to evaluate the energy and interaction pattern [14,15]. The 2D structure of bioactive compounds was retrieved from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). Meanwhile, the 3D structure of the target protein was built from SWISS MODEL (https://swissmodel.expasy.org/). In the initial stage, the ligands and protein structures were optimized before molecular docking processes. Afterward, ligands and protein were docked by PyRx 8.0 program [16]. Docking results were then visualized by PyMOL software, and the molecular interaction between the ligand and protein was assessed by LigPlot program.

RESULTS AND DISCUSSION

Molecular docking results demonstrated binding affinity scores and chemical interaction between the ligands and target protein. Computation analysis showed the Theaflavin-3-Gallate, Asiaticoside, and Theaflavin-3,3-Digallate are the top three bioactive compounds that have the lowest value of binding affinity energy (Table 1). According to the data, these results suggest that Theaflavin-3-Gallate is the most favorable compound to have the most significant interaction with the targeted protein compared to other bioactive compounds. Moreover, the Theaflavin-3-Gallate interaction has a hydrophobic bond to Tyr 195B and Lys143B residual amino acid (Fig. 1). Hydrophobic and hydrogen bond has a crucial role in maintaining protein stability [17]. Therefore, from this computational view, the Theaflavin-3-Gallate is one of the most significant candidates as drug-like compounds that can be used to reduce the leading cause of respiratory disorder caused by cigarette smoking through inhibiting the nicotine interaction to α-3 NAChR.

TABLE 1. Several bioactive compounds can interact with α-3-NAchR as the target protein. These compounds may have potency as α-3-NAchR inhibitor to avoid the adverse effect of nicotine.

BIOACTIVE COMPOUND	PLANT SOURCE	MW (g/mol)	PUBCHEM ID	BINDING AFFINITY
Theaflavin-3-Gallate	*Camelia sinensis*	704.64	71307578	-12.7 kcal/mol
Asiaticoside	*Cantella asitica*	959.13	108062	-12.2 kcal/mol
Theaflavin-3,3-Digallate	*Camelia sinensis*	868.71	21146795	-11.7 kcal/mol
Theaflavin	*Camelia sinensis*	564.50	135403798	-10.6 kcal/mol
Orthosiphol B	*Orthosipon aristatus*	676.75	15385859	-9.8 kcal/mol
(-)-Epicatechin-Gallate	*Camelia sinensis*	442.38	107905	-9.6 kcal/mol
Ellagic acid	*Moringa oleifera*	302.20	5281855	-9.0 kcal/mol
Panduratin A	*Kaempferia pandurata*	406.52	6483648	-9.0 kcal/mol
Hydroxypanduratin A	*Kaempferia pandurata*	392.49	636530	-8.9 kcal/mol
Quercetin	*Moringa oleifera*	302.24	5280343	-8.5 kcal/mol
Glucosinolates	*Moringa oleifera*	448.46	6537198	-8.1 kcal/mol
Kaempferol	*Moringa oleifera*	286.24	5280863	-7.9 kcal/mol

The use of medicinal plants has been mushrooming recently. Several common types of medicinal plants such as *Camelia sinensis, Moringa oleifera*, *Cantela asitica, Orthosipon aristatus,* and *Kaempferia pandurata* were massively consumed as supplementary food and drink. To be more specific, *Camelia sinensis* belongs to the Theaceae group. Globally, tea is the most popular consumed drink after water [18]. In the matter of facts, *Camelia sinensis* contains pretty much beneficially compounds such as Caffeine, Chlorogenic Acid, Gallic Acid, Theobromine, Pectin, Theaflavin-3-gallate, Theanine, Thearubigin, Theophylline, Theaflavin 3,3'-digallate, Theaflavins, (-)-Epigallocatechin gallate, (-)-Epigallocatechin, (-) Epicatechin gallate, (-) Epicatechin gallate, and (-) Epicatechin [9]. On the other hand, *Moringa oleifera*, a species of Moringacae family, has been known as the most cosmopolite plant

widely distributed in almost all areas, including Asia and Africa. Importantly, *Moringa oleifera* not only serves as supplementary food but also becomes the source of traditional medicine that ameliorates numerous types of diseases [19]. Another report demonstrated that *Moringa oleifera* possesses multi-therapeutic potencies as anti-inflammatory, anti-hyperglycemic, and antitumor [20]. Due to its healing potencies, *Moringa oleifera* contains numerous bioactive compounds, including Ellagic acid, Quercetin, Glucosinolates, Kaempferol, Niazimicin, Caffeic acid, Moringin, Gallic acid, Linoleic acid, Oleic acid, Linolenic acid, Eugenol, D-allose, and Ascorbic acid [10-12]. Moreover, the other plants like *Cantela asitica*, *Orthosipon aristatus*, and *Kaempferia pandurata* widely used as polyherbal medicine. Recently, polyherbal medicine gained more attention as a supplementary therapeutic strategy to overcome several types of diseases. Due to its medical potencies, these polyherbal plants contain several bioactive compounds such as Asiaticoside, Orthosiphol B, Panduratin A, and Hydroxypanduratin [13].

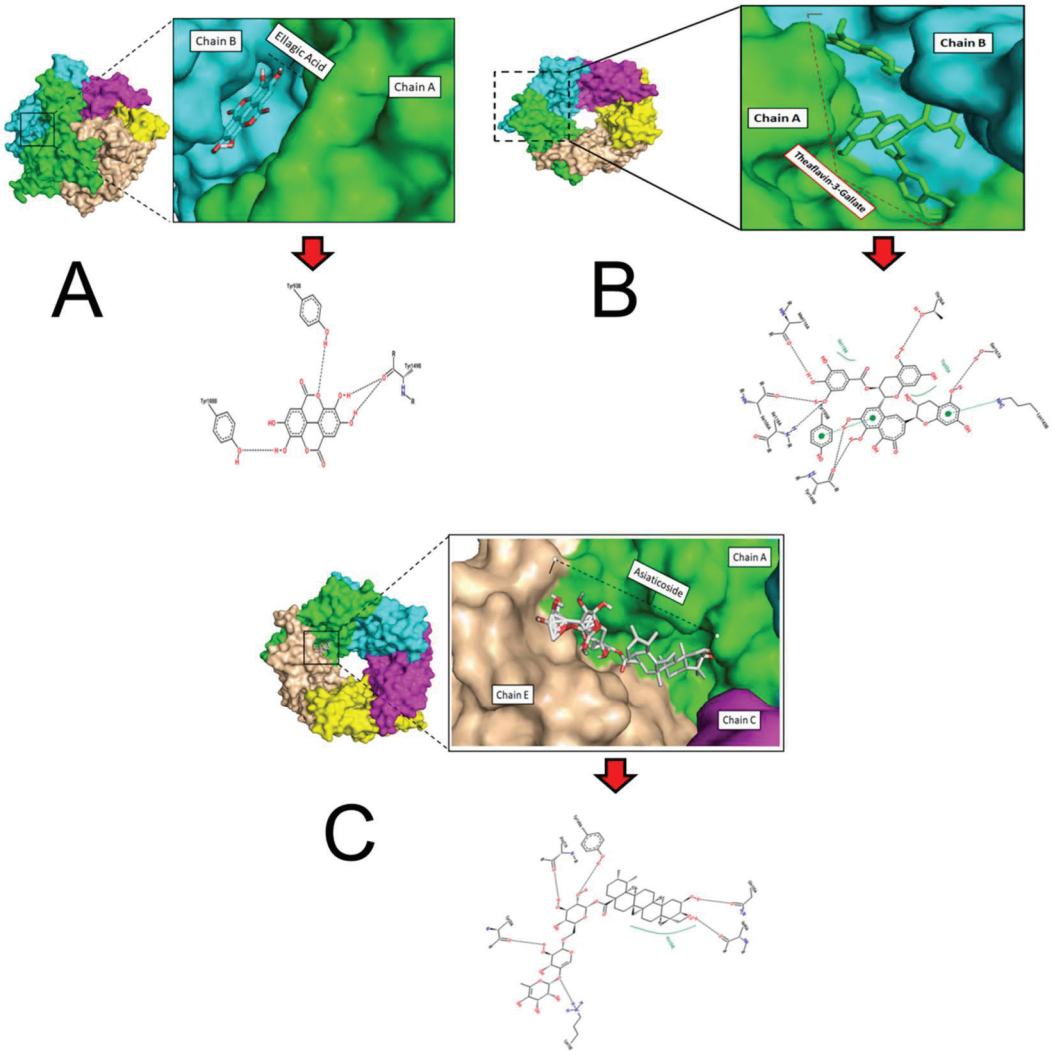

FIGURE 1. Diagram showed molecular interaction between the Ellagic acid to the α-3 NAChR (A), Theaflavin-3-Gallate to the α-3 NAChR (B), and Asiaticoside to the α-3 NAChR (C). The hydrophobic binding has a crucial role in interaction stability.

SUMMARY

According to the above prediction, three potential bioactive compounds have the most significant binding affinity, namely, Theaflavin-3-Gallate, Asiaticoside, and Theaflavin-3,3-Digallate. Eventually, further research on the specific effects and efficacy of each compound against the α-3 NAChR is necessary.

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