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RESEARCH ARTICLE

In-silico Docking and ADMET: Recent Innovations of Carvone

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ABSTRACT

For the almost 500 decades, naturally occurring plant products always showed a narrative role to society for their effectiveness against several diseases. Carvone is a mono-terpenoid which is obtained as an essential oil obtained from *Anethum graveolens* (dill) and *Carum carvi* (caraway) oils, S(+) enantiomer and the (-R) enantiomer of carvone as a primary constituent of *Mentha spicata* (spearmint) oil also found in *Calamintha officinalis* (calamint) oil. As Carvone has shown a very less toxic effect.

S(+) Carvone also acts as an anti-epileptic agent, (S & R) Carvone has shown much more potent activity when compared to (R) species of carvone. By performing In-silico docking studies of S(+) Carvone it has been observed that it is quite safe and potentially effective as an anticonvulsant agent, antispasmodic agent, antifungal agent, also as a cardiovascular agent etc. Carvone has a high permeability to GI absorption and also it follows the Lipinski rule (0 violations). Although, Carvone has less toxicity while crossing the blood-brain barrier. Docking studies of carvone is suggesting that it can be used for many advancements of the drug to achieve potent results in different pharmacological aspects.

Keyword: Carvone, S(+) Carvone , Anti-convulsant, Antispasmodic.

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INTRODUCTION

Naturally occurring products have received special attention in the preparation of novel preventives and therapeutic agents. Particularly, more natural products were identified with potential activity against many diseases. In-silico docking studies demonstrate the easy and compatible way to identify the potent moiety with the best binding energy and biological activity, protein used in this research article JNK protein, Survivin, and on some sites as anti-oxidants. ADMET has been performed from the online software Swiss ADME & ProTox-II helped for predicting the toxicity of S(+) Carvone. Carvone is used as a flavoring agent, an anti-flatulent agent, and a spice, and also used as a source of medicine for many inflammatory and congenital diseases.

Caraway (Carum carvi L.) is a biennial herb and belongs to the family Umbelliferae or Apiaceae. The genus Carum has 20 species of flowering plants. Only the genus Carum has economic importance out of its all species. C. carvi seeds have been used for flavoring, and as a spice, and the oil of caraway is used for liquors, and toothpaste, and as a flavoring agent in different food products. It prefers cool temperate zones, meadows, and fields.[1] Essential Oils and their constituent compounds have unique chemical properties that make them good candidates for drug design. Since the plant enzymes that produce terpenes are stereoselective, many EOs contain only one enantiomer of a compound. Carvone is a monoterpene ketone found in mint plants and some Mediterranean spices. S (+) enantiomer is the primary chemical constituent of Anethum graveolens (dill) and Carum carvi (caraway) oils, while the R (+) enantiomer is the primary constituent of Mentha spicata (spearmint) oil and can also be found in some chemotypes of Calamintha officinalis (calamint) oil.[2,3]

Carum carvi seeds contain 1–9% essential oils consisting of more than 30 compounds. Carvone and limonene account for the main portions.[4–7] However, the chemical groups isolated from the oils of the seeds of Carum carvi included monoterpene hydrocarbons, oxygenated monoterpenes, oxygenated sesquiterpenes, saturated and unsaturated fatty acids, aldehydes, ketones and esters.[8–16] The essential oil compounds were included (%) α-Pinene 0.3, Camphene 0.2, β-Pinene 0.1, β-Myrcene 0.1, Limonene 5.1, γTerpinene 12.6, β-Ocimene 0.1, p-Cymene 0.1, Terpinolene 0.1, limonene oxide 0.1, Camphor 0.2, Linalool 0.7, Linalyl acetate 0.3, Terpinene-4-ol 0.1, βCaryophyllene, Dihydrocarvone 0.2, α-Terpineol 0.1, Germacrene-D 0.1, Carvone 70.1, β-Selinene 0.2, αFarnesene 0.4, Citronellol 0.1, δ-Cadinene

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0.3, γ-Cadinene 0.5, Cuminaldhyde 0.1, Nerol 0.2, Trans-carveol 0.1, Nonadecane 0.1, Spathulenol 0.3, Eugenol 0.2, Thymol 0.5 and Carvacrol 0.2.[17] However, the same compounds with fluctuated percentages were recorded by other studies.[18–20] An aromatic compound, glucoside, were isolated from the water-soluble portion of the methanolic extract of caraway fruit (Carum carvi L.). Their structures were clarified as 2-methoxy-2-(4'- hydroxyphenyl)ethanol, junipediol A 2-O-beta-Dglucopyranoside and L-fucitol.[21] The flavonoid constituents of caraway were included quercetin-3-glucuronides, isoquercitrin, quercetin 3-0 caffeylglucoside, and kaempferol 3-glucoside.[22] The nutritional analysis of Carum carvi seeds (100g) showed that they contained water 9.87 g, energy 333 kcal, protein 19.77g, total lipids (fat) 14.59 g, carbohydrates, by difference 49.90g, fiber, total dietary 38.0g, sugars, total 0.64g, Calcium 689 mg, Iron 16.23mg, magnesium 258mg, phosphorus 568mg, potassium 1351mg, sodium 17mg, zinc 5.50mg, total ascorbic acid 21.0 mg, thiamine 0.3606mg, riboflavin 0.379mg, niacin 3.606mg, vitamin B6 0.360mg, folate 10µg, vitamin A (RAE) 18µg, vitamin A (IU) 363IU, vitamin E 2.50mg, vitamin, fatty acids, total saturated 0.620g, fatty acids, monounsaturated 7.125g and fatty acids polyunsaturated 3.272g.[22]

MATERIAL AND METHOD

Two-dimensional structures were drawn with the help of Cambridge software, that is, ChemDraw. Docking calculations were proceeded by using Autodock software (version 4.2). A model of JNK protein, Survivin Protein & Anti-oxidants was used as a receptor. Grid box values for each ligand's ideal grid were assigned using AutoDock4.2, and they were discovered through trial and error and earlier research. Points were created for grid maps, and the grid point spacing was 0.375. To carry out the molecular docking investigations, the Lamarckian Genetic Algorithm (LGA), regarded as one of the finest docking techniques accessible in AutoDock, was used. The following criteria for LGA were established: a maximum of 250,000 energy assessments. Based on the binding energy, the docked conformations of the two isomers were grouped into clusters, and each conformation was then visually examined using Discovery Studio 2021. However, human and drug resources would certainly be wasted while the molecule is being cleared for use in clinical studies. As a crucial tool for predicting the toxicity of compounds that could be detrimental to people, animals, plants, and the environment, In silico toxicity is constantly developing. The purpose of in silico toxicity models is to supplement the current in vitro toxicity methodologies to anticipate the toxicity effects of chemicals, hence reducing the time, the necessity of animal testing, and the related costs. The information from several domains, including toxicology, biostatistics, systems biology, computer science, and many other pertinent disciplines, is included in the in silico toxicity model. A chemical's toxicity can be assessed using toxicity endpoints including mutagenicity, carcinogenicity, and a variety of other endpoints. Additional measurements include LD50 (lethal dosage) values and binary (active/passive) measurements. Initially, ProTox: a website for the prediction of rat oral toxicity was launched in the year 2014 to make a rodent acute toxicity prediction platform accessible to a broader audience, both experimental researchers and computational toxicologists. Comparatively, ProTox approaches outperformed commercial online software Pro Tox-II.

Molecular Docking Studies

To investigate the mechanism of interaction between inhibitors and receptor sites, molecular docking experiments were examined. The ability to anticipate how compounds will interact with their targets is crucial in the drug development process. When compounds are docked with protein targets, the processes of selectivity may be discovered with ease.. In this work, the activity of Carvone was screened out against the target sites as JNK protein (2WAJ as protein binding site, with the active amino acid; Lys:93, Anisomycin as standard) Anti-oxidant (1HD2 as protein binding site, with the active amino acid; Cys:47 & Cys:151, Hydroxy Benzoate as Standard) Anti-Cancer (1E31 as protein binding site, with the active amino acid; Thr:34 & Iso:19 …….. as Standard). The effects of several docking parameters, including FF (kcal/mol), G (Gibb's free energy), ligand solvation energy, hydrogen bonding (interactions), and others, were examined. The analysis of all feasible binding modalities was done based on FF and cluster formation. Hydrogen bonding (interactions) and the FF score were used to rate each output cluster. The ideal FF score is regarded as a minimal cluster rank. If a molecule's FF score has a higher negative value, it is considered to have more advantageous binding modes and a better fit. The discussion will focus on the docked conformations with the lowest binding energies. However, if a molecule has a low docking score for the most advantageous interaction, it is considered to have a greater binding affinity of ligands for that interaction.

Pharmacophore of Carvone

Pharmacophore modeling of Carvone tells us about the structure, that which part of the moiety is responsible for active desired therapeutic activity or response Figure 1.

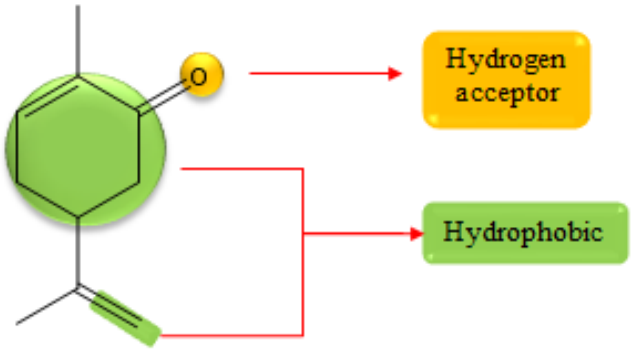


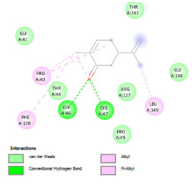
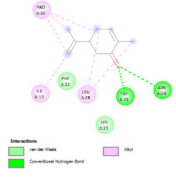
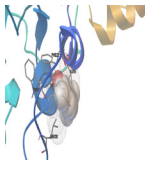
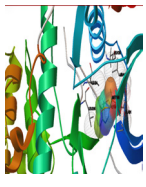
Figure 1: Pharmacophore of S(+)Carvone

Docking

With the help of AutoDock4.2, both the isomers were docked with the receptor sites as JNK protein (2WAJ as protein binding site, with the active amino acid; Lys:93, Anisomycin as standard) Anti-oxidant (1HD2 as protein binding site, with the active amino acid; Cys:47 & Cys:151, Hydroxy Benzoate as Standard) Anti-Cancer (1E31 as protein binding site, with the active amino acid; Thr:34 & Iso:19 Doxorubicin as Standard)

While docking S(+) Carvone with the respective receptors. We get the Results (Table 1);

Table 1: 2D &3Dresults of carvone

PDB file used to dock	*Ligand*	*3D Result*	*Binding Energy*	*Ligand (Binding residues)*
1HD2 (Anti-oxidant)			-4.62	CYS A:47 GLY A: 46 PRO A:40 PHE A:120 LEU A: 149
1E31 (Anti-cancer)			-4.13	TRP A:25 ASN A:24 PRO A:35 ILE A: 19 LEU A: 28
2WAJ (JNK)			-5.82	LYS A:93 LEU A: 206,144, 126 VAL A:78 ALA A:91 MET A:146

ADMET Studies

The Swiss ADME online Web service predicted the physicochemical parameters of Carvone, including the commercially available anticancer, and anti-epileptic medicines. Swiss ADME, an online application, was used to create a streamlined molecular input line entry method for Carvone analysis of ADME.

The capacity of gastrointestinal (GI) absorption and the permeability of the blood-brain barrier were additional predictions made by the BOILED-Egg model of the molecules. Several methods—namely, Lipinski's rule of five (ROF), the bioavailability score, Ghose's rules, and Veber's rules—were used to determine the cutoff values for the physicochemical attributes. The molecular characteristics MW (molecular weight), HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), log P (lipophilicity log), log S (aqueous solubility), TPSA (topological polar surface area), nRot (number of rotatable bonds), and MR (molar refractivity) were analyzed for drug-likeliness.

BOILED-Egg for Prediction of GI Absorption and Brain Penetration of S(+) Carvone

Blood-brain barrier (BBB) penetration and GI absorption are key factors in the medication development process. Because it provides datasets with precision, speed, and understandable graphical representations, the BOILED-Egg model aids in the computation of derivative polarity and lipophilicity. By sifting through chemical libraries, this approach aids in the creation of new drugs. In the Figure 2, BOILED-Egg model, the white zone (yolk) indicates the high likelihood of BBB penetration, whereas the yellow region (white) represents the high probability of the GI tract's passive absorption of Carvone. Additionally, the P-glycoprotein actively effluxes the molecule as shown by the blue color indicator of the molecule, which is represented as (PGP+), as opposed to the red color indication, which indicates the nonsubstrate of P-gp, which is indicated by the blue color indicator as (PGP).

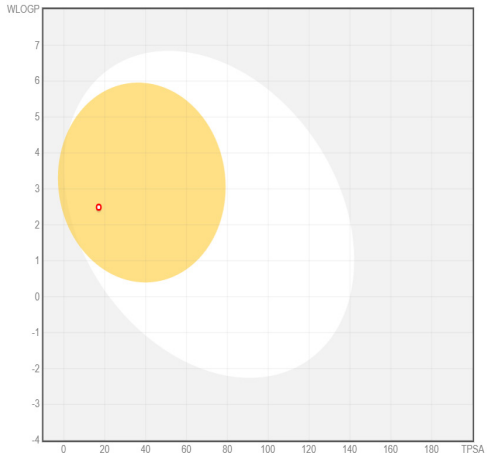


Figure 2: Boiled Egg diagram showing good BBB penetration power of S(+) Carvone

Toxicity Prediction by using ProTox-II

Compared to current computational models, the ProTox-II web server offers several benefits. Chemical

and molecular target knowledge is included on the ProTox website. The ProTox-II webserver is unique in that the prediction scheme is broken down into various levels of toxicity, such as oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints (such as mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity), toxicological pathways (AOPs), and toxicity targets, thereby revealing potential molecular mechanisms underlying such toxic responses. The updated version, ProTox-II, adds chemical similarity, fragment propensities based on pharmacophores, most prevalent characteristics, and machine learning models for the prediction of multiple toxicity endpoints. The most toxicological endpoints have been predicted by the model. Toxicity prediction website free computational tool called ProTox-II.

Input parameter

The ProTox-user II's interface is intuitive and simple to use. The user can enter the compound's name or its SMILES (Simplified Molecular-Input Line-Entry System) string to forecast probable toxicities related to its chemical structure. Additionally, the user has access to the chemical editor on https://www.chemdoodle.com, which enables them to create the chemical structure. Furthermore, the user may search for chemical structures using a compound name utilizing the integrated PubChem search (https://pubchem.ncbi.nlm.nih.gov/). The user has the choice of choosing additional models, or all models, for prediction. The website computes the prediction for acute toxicity and toxicity targets by default if the user does not specify any extra models.

Output information

Instantaneously generated prediction findings for the acute toxicity and toxicity targets. The projected median fatal dosage (LD50) in mg/kg weight, the toxicity class, the prediction accuracy, the average similarity, and the three most comparable dangerous substances from the dataset with the known rat oral toxicity value are all displayed on the result page. If the information on anticipated toxicity targets is available, it will be displayed along with the target's name, average fit, and degree of similarity to the target's pharmacophore and known ligands. In addition, the result page will display a table with the forecast outcomes and confidence score for each extra model the user has chosen. The outcomes will be accessible via a web link. Acute toxicity (oral toxicity model with six distinct toxicity classes), organ toxicity, toxicological endpoints (four models), toxicological pathways, and toxicity targets are the five categorization phases that make up the ProTox-II platform. Each model is well described and is accessible through the ProTox-II service. On the ProTox-II website, under model details, resulted in data will contain comprehensive information including references, performance scores, and frequency distributions of the most prevalent characteristics contained in the training set (both for active and inactive molecules).

Acute toxicity

Oral toxicity

According to our earlier study, the acute toxicity models are based on chemical similarities between substances with known harmful effects and the existence of dangerous fragments.[23] The upgraded version of the internal database SuperToxic is where the acute toxicity statistics are taken from.[24]

Toxicity targets

The Novartis in vitro safety panels of the protein targets connected to unfavorable drug responses.[25] are used as the basis for the prediction of toxicity targets. These targets were previously described in our earlier research.[26]

Organ toxicity

Hepatotoxicity

One of the main causes of the recall of pharmaceuticals from the market is drug-induced hepatotoxicity, which is a substantial cause of abrupt liver failure.[27] Drug-induced liver damage (DILI) might be an uncommon occurrence or a long-term trend. But for drug makers, regulators, and doctors, the ability to forecast DILI is crucial and one of the major concerns.[28] The NIH LiverTox database and DILIrank.[29] are the sources of the data used for DILI prediction.[30] On cross-validation, the ProTox-II hepatotoxicity prediction model has a balanced accuracy of 82%.

Toxicological endpoints

Carcinogenicity

Carcinogens are substances that can cause tumors or increase the frequency of malignancies. (19). Data for predicting carcinogenicity are gathered from the CEBS database and the Carcinogenic Potency Database (CPDB).[31,32] A balanced accuracy of 81.24 percent on cross-validation and 83.30 percent on external validation characterizes the ProTox-II carcinogenicity prediction model. Cross-validation and external validation had AUC-ROC values of 0.85 and 0.87, respectively.

Mutagenicity

Mutagens are substances that alter a cell's DNA or induce other aberrant genetic alterations.[33] These alterations

may injure the cells and result in conditions like cancer. ProTox-ability II's to forecast mutagenicity is based on benchmark data from the Ames test[34] and the CEBS database.[34] A balanced accuracy of 84.00 percent on cross-validation and 85.00 percent on external validation characterizes the ProTox-II mutagenicity prediction model. Cross-validation and external validation each get AUC-ROC values of 0.90 and 0.91.

Cytotoxicity

It's crucial to predict cytotoxicity when screening chemicals for the latter, as in the case of tumor cells, intended cell harm (1). Data taken from the database of the Chemical European Biology Laboratory (ChEMBL) form the basis of the ProTox-II cytotoxicity model.[35] All substances are regarded as positively cytotoxic if their in vitro toxicity test results against HepG2 cells show an IC50 value of less than or equal to 10 M. A balanced accuracy of 85.00 percent on cross-validation and 83.60 percent on external validation characterizes the ProTox-II cytotoxicity prediction model. Cross-validation and external validation each get AUC-ROC values of 0.89 and 0.90'

Immunotoxicity

The adverse effect of xenobiotics on the immune system is called immunotoxicity.[36] The immunotoxicity model is based on immune cell cytotoxicity data obtained from the U.S. National Cancer Institute's (NCI) public database. Growth inhibition (GI50) values from the B-cell line RPMI-8226 are used and compounds with GI50 values below 10 μM are defined as toxic. The ProTox-II immunotoxicity prediction model has a balanced accuracy of 74.00% on cross-validation and 70.00% on external validation. The AUC–ROC scores of cross-validation and external validation are 0.76 and 0.74 respectively of S (+) Carvone.

Prediction models

On the ProTox-II platform, all recently updated prediction models are built using machine learning techniques. The categorization and prediction models for hepatotoxicity, cytotoxicity, mutagenicity, and carcinogenicity are built using the Random Forest (RF) algorithm.[37] GINI index criteria and 500 decision trees are used to build the RF-based models. Utilizing an RF-based classifier has the benefit of frequently preventing overfitting. RF and Support Vector Machine (SVM) classifiers are utilized as a part of an ensemble strategy to create the Tox21-based toxicological pathway prediction. The SVM algorithm uses the radial basis function (RBF) as its kernel function. According to the published work, the Bernoulli-Naive Bayes algorithm serves as the foundation for the immunotoxicity prediction model.

RESULT AND DISCUSSION

The main emphasis has been on defining the physicochemical property rules for the derivatives to reduce attrition and increase the likelihood of them at various stages of anti-epileptic, anti-cancer, etc in drug development. To accurately access drug-likeness, Lipinski's RO5, Ghose filter, Vebers's, Egan's, and Muegge's rules are compared with certain marketed drugs' Physiochemical properties. Lipophilicity, water solubility, drug-likeness, etc are the parameters used to determine the ADME property of S(+) Carvone. By performing a docking study we got the binding energy of -4.62kcal/mol, -4.13kcal/mol &-5.82kcal/mol with the protein binding sites anti-oxidant, anti-cancer, and JNK protein (anti-epileptic activity) respectively. So, when the in-silico study of S(+) Carvone was performed by using AutoDock4.2, Swiss ADME (Table 2), and ProTox-II, (Table 3 and Figure 3) it has been analyzed that S(+) Carvone can be used for enhancing many drug's therapeutic index also by decreasing it's toxicity drug class IV.

Table 2: Various parameters required to analyze the Carvone as a safe moiety.

Physiochemical Properties Of Carvone	Lipophilicity Of Carvone	Water Solubility Of Carvone	Pharmacokinetics of Carvone	Drug-likeness of Carvone	Medicinal Chemistry
Formula: C10H14O Molecular weight: 150.22 g/mol No of. heavy atoms: 11 No. of arom. heavy atoms:0 No. of rotatable bonds: 1 No.of H-bond acceptors: 1 No. of H-bond donors:0 Molar Refractivity:47.32	Log $P_{o/w}$ (iLOGP) :2.27 Log $P_{o/w}$ (XLOGP3) : 2.71 Log $P_{o/w}$ (WLOGP):2.49 Log $P_{o/w}$ (MLOGP):2.10 Log $P_{o/w}$ (SILICOS-IT):2.64 Consensus Log $P_{o/w}$:2.44	Log *S* (ESOL): -2.41 Solubility: 5.81e-01 mg/ml ; 3.87e-03 mol/l Class: Soluble Log *S* (Ali) : -2.72 Solubility : 2.85e-01 mg/ml ; 1.90e-03 mol/l Class: Soluble Log *S* (SILICOS-IT) :-2.16 Solubility:1.04e+00 mg/ml ; 6.95e-03 mol/l Class: Soluble	GI Absorption: High BBB Permeant: Yes P-gp substrate: No CYP1A2 inhibitor: No CYP2C19 inhibitor: No CYP2C9 inhibitor: No CYP2D6 inhibitor: No CYP3A4 inhibitor: No Log K_p (skin permeation):-5.29cm/s	Lipinski: Yes;0 Violation Ghose: No, 1 violation: MW<160 Veber: Yes Egan: Yes Muegge : No; 2 violations: MW<200, Heteroatoms<2 Bioavailability Score:0.55	PAINS:0 Alert Brenk: 1 alert: isolated_alkene Leadlikeness: No; 1 violation: MW<250 Synthetic accessibility:3.33

When toxicity prediction was performed by using, ProTox-II.We got predicted LD50:1640mg/kg, and predicted toxicity Class:4 as a result. Also, Data presented in Table 3 & Figure 3 (Radar Chart) demonstrates all toxic active and inactive sites of Carvone

Table 3

Mol weight	***150.22***
Number of Hydrogen bond acceptors	15
Number of Hydrogen bond donors	0
Number of atoms	25
Number of rotatable bonds	1
Molecular refractivity	47.32
Topological Polar Surface Area	17.07
Octanol/water partition coefficient (log P)	2.49

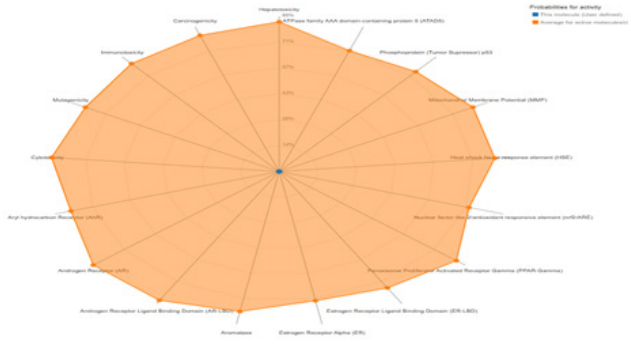


Figure3: Radar Chart of Carvone's toxicity

CONCLUSION

In the above study, in-silico docking &ADMET studies, it has been found that S(+) Carvone is a potential molecule with no toxicity,it also crosses BBB. The permeability of BBB additive prediction made by Boiled egg also,it follows Lipinski RO5.On docking of S(+) Carvone with the respective receptor, the obtained results with good binding scores have suggested that S(+) Carvone is a potential moiety. This enantiomer of Carvone can be used for further research purposes as anti-epileptic activity.

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