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The Effect of Structural Modification on the Blood Brain Barrier Permeation Properties of Allicin

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Authors' contributions

This work was carried out in collaboration among all authors. Author VEI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FAI and OJU managed the analyses of the study. Authors DAC and CS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Allicin is found in nursery onion. Allicin is isolated from garlic (Allium sativum). Nutriceutical allicin is an organice compound gotten from garlic. It is also sourced from onions, and different species in the family Alliaceae. It was first isolated and examined in the research facility by Chester J. Cavallito in 1944. This colourless fluid has a distinctively pungent smell. This compound shows antibacterial and anti-fungal properties. Allicin is additionally the garlic's resistance mechanism against assaults by pests. In this investigation, we considered the impact of the substitution of a terminal methyl group of allicin with hydroxyl group. The 2D structure of Allicin and its analogue were designed by utilizing the ChemAxon programming and spared as mrv files. The mrv file were changed over into SMILES strings utilizing the OpenBabel programming and pharmacokinetic parameters were predicted by using the SwissADME server. Results from the investigation demonstrated that the basic change directed at the terminal methyl group of allicin converted into a non neuroactive compound with no capacity to cross the blood brain barrier.

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Keywords: Allicin; garlic; pharmacokinetics; blood brain barrier.

1. INTRODUCTION

Allicin is an organosulfur compound gotten from garlic, a species in the family Alliaceae [1]. It was first isolated and studied in the laboratory by Chester J. Cavallito and John Hays Bailey in 1944 [2,3]. At the point when crisp garlic is chopped or squashed, the enzyme alliinase converts alliin into allicin, which is responsible for the Aroma of fresh garlic [4]. The allicin generated is unstable and rapidly changes into a progression of other sulfur-containing compound, such as diallyl disulfide [5]. Allicin is part of a resistance mechanism against attacks by bugs on the garlic plant [6].

Allicin highlights the thiosulfinate functional group, R-S (O)- S-R. The compound is absent in garlic except if tissue damage occurs [1], and is formed by the activity of the enzyme alliinase on alliin. Allicin is chiral yet occurs normally just as a racemate [3]. The racemic structure can likewise be produced by oxidation of diallyl disulfide [7]. Alliinase is irreversibly deactivated below pH 3 and as such, allicin is generally not produce in the body from the consumption of fresh or powdered garlic [8,9]. Moreover, allicin can be unstable, breaking down within 16 hours at 23°C [10].

Allicin is an oily, somewhat yellow fluid that gives garlic its interesting scent. It is a thioester of sulfenic acid and is otherwise called allyl thiosulfinate [11]. Its biological activity can be credited to the two its antioxidants activity and its reactions with thiol-containing proteins [12]. In the biosynthesis of allicin (thio-2-propene-1-sulfinic corrosive S-allyl ester), cysteine is first converted into alliin. The enzyme alliinase, which contains pyridoxal phosphate (PLP), divides alliin, producing allysulfenic acid, pyruvate, and ammonium [12]. At room temperature allysulfenic acid is unsteady and exceptionally reactive, which prompt two particles of it to spontaneously combine in a dehydration reaction to form allicin [11].

Produced in garlic cells, allicin is discharged upon disruption, creating a potent characteristics aroma when garlic is cut or cooked [5,6]. Allicin has been studied for its ability to treat different sorts of multiple drug resistance bacterial infections, just as viral and parasitic diseases in vitro, however as at 2016, the wellbeing and viability of allicin to treat diseases in individuals was misty [13]. In a small clinical trial, an everyday high dose of extracted allicin (multiple times the sum in a garlic clove) demonstrated adequacy to preventt the normal cold [14]. A Cochrane audit saw this as insufficient to make conclusion [15].

This study is aimed at exploring the impact of structural modification on the blood brain barrier penetration properties of allicin.

2. METHODS

2.1 Ligand Planning

The 2D structure of allicin and its analogue were designed using the ChemAxon programming [16]. All designed structures were downloaded and saved as mrv files in anticipation of docking [17].

2.2 File Conversion

Saved mrv files from the designed ligands were converted into SMILES strings (Simplified Molecular Input-Line-Entry System) by using the Open Babel Open Source Chemistry Toolbox. Open Babel, a chemical toolbox is designed to speak many of the languages of chemical data [18]. This is an open and collaborative project allowing anyone to make searches, conversions, analysis, or storage data from molecular modeling, chemistry, solid state materials, biochemistry, or related regions [19].

2.3 Minimization of Ligands

Allicin and its analogue were minimized by using the UCSF Chimera software [20]. UCSF Chimera is an extensible program for analyzing and intuitively envisioning molecular structures and related data which include supramolecular assemblies, density maps, alignment of sequences, results from molecular docking, trajectories and conformational ensembles [21,17].

3. RESULTS AND DISCUSSION

The polar surface area (PSA), also known as the topological polar surface area (TPSA) of a molecule is defined as the entirety of every single polar molecule (oxygen and nitrogen), with the inclusion of the hydrogen atom attachments. The polar surface area is a metric that is often used in

medicinal chemistry to optimize the cell permeation ability of drugs. Molecules with a PSA value higher than 140 angstroms squared are known to be poor in cell membrane penetration [22]. For molecules to penetrate the blood–brain barrier (BBB) in order to act on the central nervous system receptors, the value assigned to the polar surface area should be less than 90 Å squared [23]. The TPSA value of allicin is 61.58 Å, hence its ability to cross the blood brain barrier as the value appeared to be lower than 90 Å.

The segment coefficient between n-octanol and water (log Po/w) fills in as the old style technique for the portrayal of lipophilicity. The decent variety of the models backing the indicators will expand the precision in the forecast utilizing the consensus log Po/w [24]. The lipinski's standard [25] was utilized as the drug similarity descriptor with the end goal of this examination and the ideal lipophilicity range (Log Po/w) permitted ought not to surpass 5. The perception from the concensus lipophilicity section of Fig. 3A and 3B demonstrates that allicin and its OH subsidiary derived are within the ideal lipophilicity range and as such can be regarded as drug-like compounds [17].

Activities regarding drug development can be facilitated and made easier in cases where molecules are soluble. This brings about ease in drug handling and its formulation [26]. Moreover, for discovery projects that target the oral form of administration, one of the major absorption property influencers the solubility of the compound [27]. Also, drugs are designed for parenteral administration, requires a high solubility attribute to aid the delivery of an appreciable amount of the active ingredient in smaller volumes of pharmaceutical dosage [28]. A compound can be considered as soluble if the Log S value is less than 6 [26]. Allicin and its OH analogue that were used for the purpose of this study, according to the column projecting the solubility result in Fig. 3A and 3B are water soluble, implying that they might be easily absorbed.

The nature of the gastrointestinal mucosal membrane surface area plays an important and srole in the process of drug absorption and it has a varying and differential effect from the stomach to the rectum. The physiochemical properties of the luminal content are also implicated to have an influence in drug absorption process [29]. The absorption process itself is continually described in terms of hypothesis of simple partition of pH, where absorption is controlled by the equilibrium position between the ionized and non-ionized forms of the drug at varying physiological pH values encountered in the gastrointestinal tract [30]. Allicin and its OH analogue possess a high gastrointestinal absorption rate, indicating their ability to aid drug bioavailability.

Overcoming the ability of a non neuroactive drug to cross the blood brain barrier is a major challenge to be solved in the processes of designing drugs. Only neuroactive drugs are required to possess the blood brain permeation attribute for functionality On the contrary, non neuroactive drugs should not cross the blood brain barrier for the avoidance of psychotropic side effects [31]. Blood-brain barrier permeation results from Fig. 3A and 3B showed that allicin lost its BBB permeation properties when one of its terminal methyl groups was substituted for hydroxyl group.

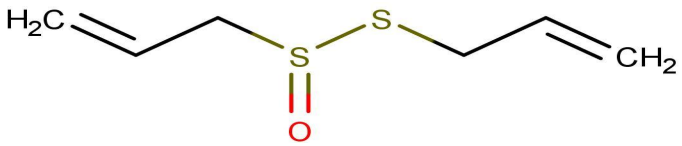

Fig. 1. 2D structure of allicin

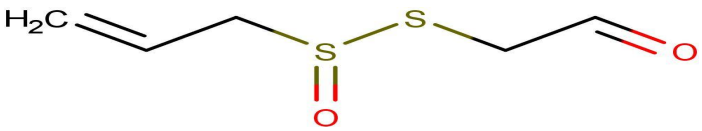

Fig. 2. 2D structure of the OH analogue of allicin

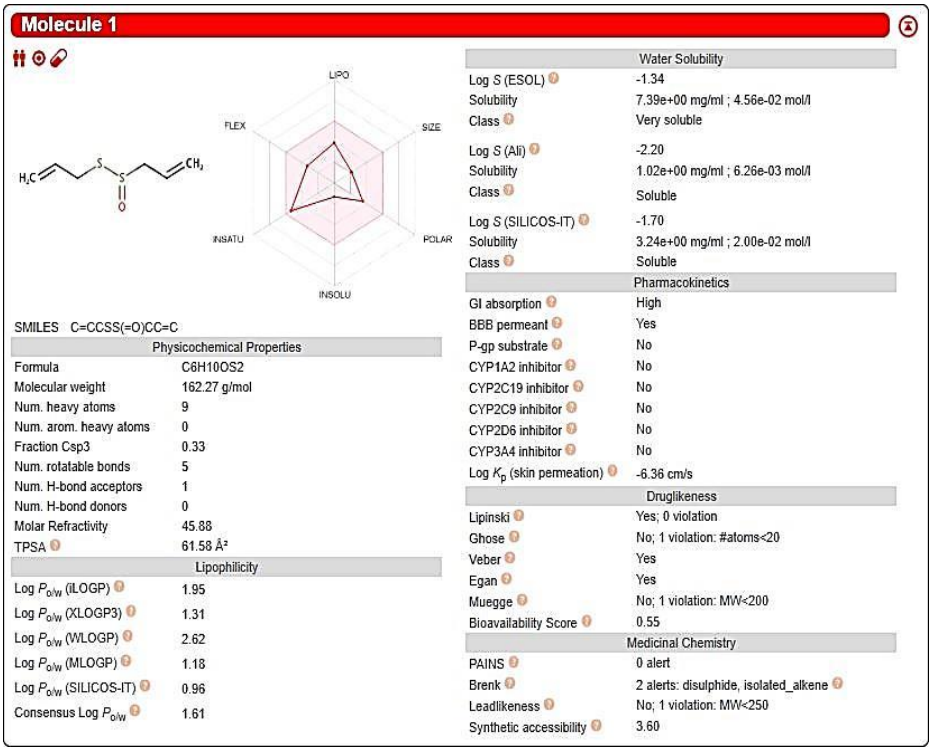

Fig. 3A. Drug likeness computation

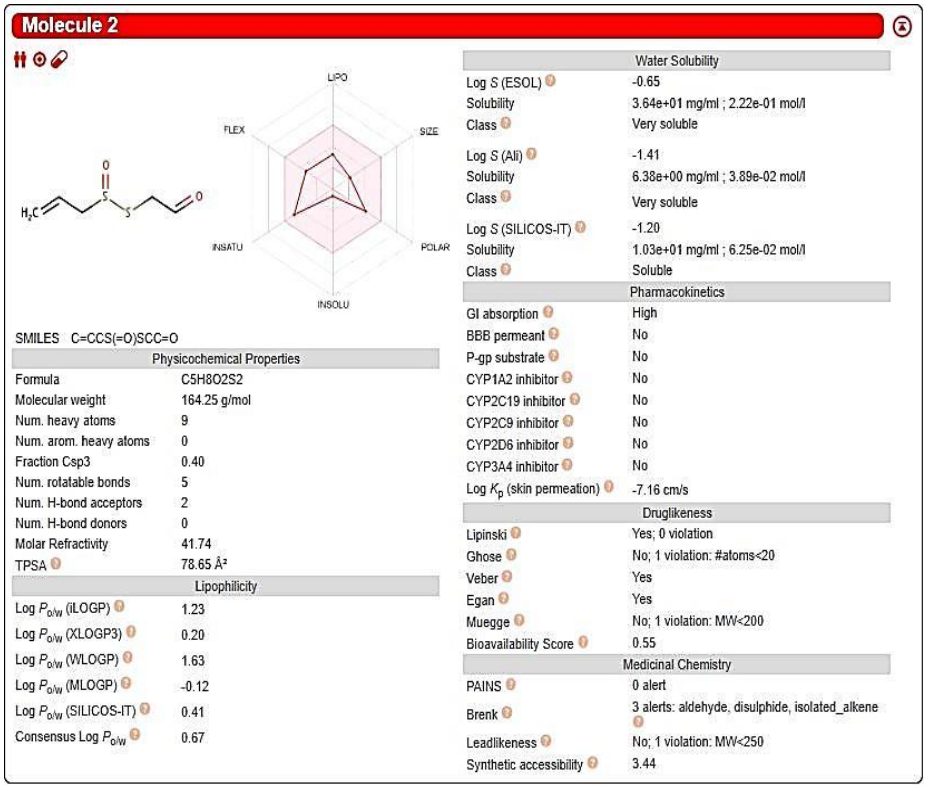

Fig. 3B. OH analogue of Allicin

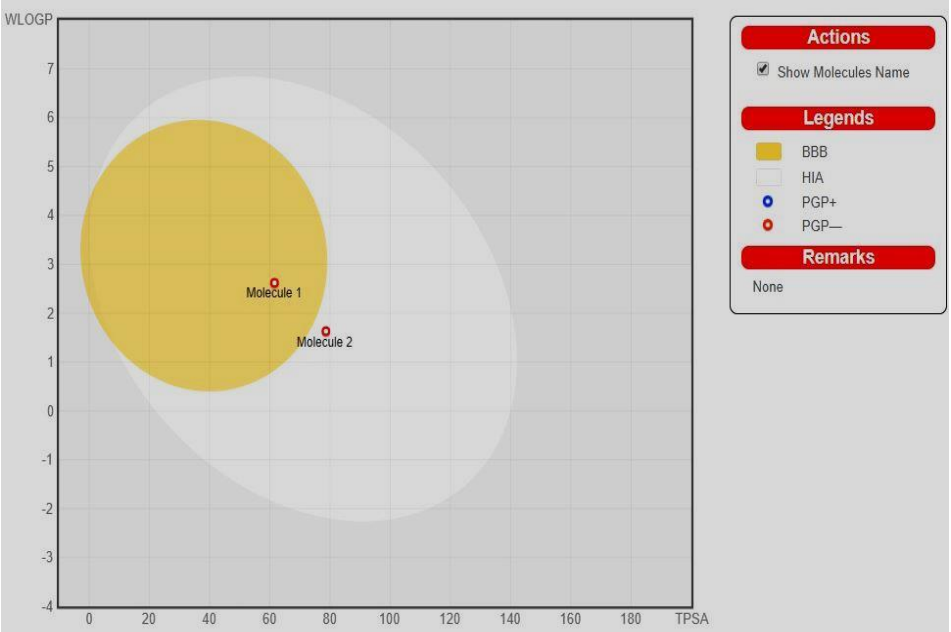

Fig. 4. Boiled-egg plot
(Molecule 1: Allicin; Molecule 2: OH analogue)

4. CONCLUSION

The overall result from this experiment demonstrates the effect of structural modification on drug like compounds. The substitution of a terminal methyl group (CH3) for hydroxyl group (OH) in allicin converted it to a non neuroactive compound. This modified version of allicin in turn can be useful in the treatment of infections that does not affect the central nervous system. We therefore recommend further modifications on this compound and molecular docking protocol against enzymatic targets to confirm the potency of the drug.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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