Computational Evaluation of Pharmacokinetics and Potential Protein Targets of Ginger (Zingiber officinale)

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ABSTRACT

Ginger, the rhizome of the Zingiber officinale, a herbaceous tropical perennial plant which belong to the family Zingiberaceae. Ginger is a non-toxic highly promising natural compound having a wide spectrum of biological functions. In this study, selected bioactive components of ginger were computationally evaluated for therapeutic potential in relevance to human diseases using standard bioinformatics tools such as Pubchem, Swisstargetprediction and Swissadme. The result of this study showed that most of the targets obtained such as 5-hydroxytryptamine receptors, carbonic anhydrases and zinc finger proteins, have not been adequately researched in relation to the therapeutic potential of ginger. Ginger showed high potential in the prevention and management of cancer, neurodegenerative dementia and cardiovascular diseases in human, which could be administered alone or in combination with other drugs.

Keyword: Ginger, Zingiber officinale, Target prediction, Computational pharmacokinetics, Human diseases, 5-Hydroxytryptamine receptors, Carbonic anhydrases, Zinc finger proteins.

INTRODUCTION

Ginger, the rhizome of the Zingiber officinale, a herbaceous tropical perennial plant which belong to the family Zingiberaceae. A numeral of commercial variety of ginger exists, and about 25 species of Zingiberaceae are used to cure multiple disorders in human and animals [1]. Nigerian ginger is darker in color, minute size and more pungent taste [2]. Ginger contains several valuable compounds and new constituents are still being found [3]. The composition varies with the type, variety, agronomic conditions, curing methods, drying and storage conditions [2].

Ginger is a non-toxic highly promising natural compound having a wide spectrum of biological functions which include; antioxidant, antihypertensive, anti-migraine, anti-osteoarthritis, anti-inflammatory, anti-tumor, antimicrobial, anti-diabetes, anti-emetic, analgesic, neuro-protective, gastro-protective, and hepatoprotective [2, 4, 5]. Ginger is well tolerated even at a very high dose without any toxic effects. Thus ginger and its bioactive components have the potential for development of modern medicine in the treatment of many human diseases.

In the post-genomic era, benefiting from the dramatic increase in bio-macromolecule and small molecule information, computational tools can be applied to most aspects of the drug discovery and development process, from target identification and validation to lead discovery and optimization; the tools can even be applied to preclinical trials, which greatly alters the pipeline for drug discovery and development. The use of computational tools could reduce the cost of drug development by up to 50% [6]. In this study, selected bioactive components of ginger were computationally evaluated for therapeutic potential in relevance to human diseases.
MATERIALS AND METHODS

**Ligands Preparation**
Nine active ingredients of ginger were selected from the available literature [2, 4, 7]. The three dimension structure in .sdf format and canonical SMILES of the ligands were obtained from NCBI PubChem Compound (http://www.ncbi.nlm.nih.gov/pccompound).

**ADME/Tox Screening**
ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) screening helps in detecting drug likeliness of compounds [8]. The SMILES format the ligands were loaded into the SwissADME server (http://www.swissadme.ch) and ADME screening was done at default parameters.

**Potential Target Analysis**
The SMILES format of all the ginger components was analyzed using SwissTargetPrediction server (http://www.swisstargetprediction.ch) [9], and Homo sapiens was selected as the source of target.

RESULTS
The result of ADME/Tox screenings of the bioactive components of ginger used in this study was summarized in table 1. The result showed that they were safe as potential therapeutic agents, with high gastrointestinal (GI) absorption and skin permeability. There were many targets obtained for each bioactive component of ginger. Those within the range of 70-100% probability were selected as showed in table 2. The targets belonged to three classes; receptors, enzymes and proteins. The result showed that most of the bioactive components of ginger are effective against similar biological target.

DISCUSSION
Ginger is one of the most commonly used herbal medicines for the treatment of numerous ailments and improvement of body functions. It may be used in combination with prescribed drugs. All the ginger components in this study as showed in table 1, obeyed the Lipinski rule of drug-likeness [10], which accounted for their high absorption, solubility and skin permeability. They have similar bioavailability score, which was a function of the rotation bonds [11]. Although, trans-12-shogaol showed one violation for Lipinski and Veber rules, it has been reported that in a successful marketed drug, one parameter can compensate for another [10]. The ADME rules and properties accounted for drug-likeness in human, but does not predicted if a compound is pharmacologically active.

The co-administration of ginger with therapeutic drugs could have synergistic in the treatment of multiples of human diseases. It has been reported that ginger component showed rapid half-life and no to low toxicity in humans [25]. The same study showed that ginger components may regulate the activity and expression of various human cytochrome P450 (CYPs), probably resulting in alternations in drug clearance and response [25].

There are experimental studies on animal model, that have showed the inhibitory potential of ginger on other targets, which include; acetylcholinesterase in relevance to Alzheimer’s disease [12], angiotensin-1 converting enzyme (ACE) and arginase in relevance to hypertension and atherosclerosis respectively [13, 14], α-glucosidase in relevance to type-2 diabetes [15]. The result of these studies indicated moderate inhibition of the targets by ginger extract, which were similar to the report of Sanghal et al [16].

The prediction of the possible target of action (table 2), showed that most of the targets such as 5-hydroxytryptamine receptors, carbonic anhydrases (CAs) and zinc finger proteins, have not been adequately researched in relation to the therapeutic potential of ginger, except lipoxygenases [4, 17-20]. Previous computational study has showed that ginger components could be optimized as lead for the treatment of neurodegenerative diseases, such as Alzheimer’s disease, because of its wide spectrum of potential targets which include acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), β-site amyloid precursor protein cleaving enzyme (BACE-1), human carboxylesterase (hCE-1), and nitric oxide synthase (NOS) among others [24]. The lipoxygenases has been reported to have intimately linked activities [21]. The report of Nievergelt et al [17] indicated that 10-shogaol, 1-dehydro-6-gingerdione, and particularly the whole lipophilic ginger extract partially activated the 5-HT1A receptor (20–60% of maximal activation). Ginger extract has been reported as an inhibitor of lipoxygenase, cyclooxygenase, interlukin, and as an activator of P53 and Bax in cancer management [4].
Table 1: ADME/Tox Screening of Selected Components of Ginger.

(Molecular weight, Heavy atom, Aromatic heavy atoms, Fraction Csp3, Rotatable bonds, H-bond acceptors, H-bond donors, Molar Refractivity, Total polar surface area, XLOGP3, ESOL Log S, GI absorption, Lipinski violations, Bioavailability Score).

<table>
<thead>
<tr>
<th>Ginger component</th>
<th>MW</th>
<th>HA</th>
<th>AH</th>
<th>FC</th>
<th>RB</th>
<th>HBA</th>
<th>HBD</th>
<th>MR</th>
<th>TPSA</th>
<th>LogP</th>
<th>LogS</th>
<th>GA</th>
<th>LV</th>
<th>BS</th>
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<tbody>
<tr>
<td>A</td>
<td>294.39</td>
<td>21</td>
<td>6</td>
<td>0.59</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>84.55</td>
<td>66.76</td>
<td>2.76</td>
<td>-2.96</td>
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<td>0.55</td>
</tr>
<tr>
<td>B</td>
<td>346.46</td>
<td>25</td>
<td>6</td>
<td>0.52</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>103.13</td>
<td>63.60</td>
<td>5.67</td>
<td>-4.88</td>
<td>High</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>C</td>
<td>276.37</td>
<td>20</td>
<td>6</td>
<td>0.47</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>82.91</td>
<td>46.53</td>
<td>6.11</td>
<td>-3.72</td>
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<tr>
<td>D</td>
<td>278.39</td>
<td>20</td>
<td>6</td>
<td>0.59</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>111.75</td>
<td>46.53</td>
<td>7.24</td>
<td>-5.82</td>
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<td>1</td>
<td>0.55</td>
</tr>
<tr>
<td>E</td>
<td>360.53</td>
<td>26</td>
<td>6</td>
<td>0.61</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>111.75</td>
<td>46.53</td>
<td>7.24</td>
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<tr>
<td>H</td>
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</tbody>
</table>

A= 6-Gingerol, B= 1-Dehydro-10-gingerdione, C= 6-Shogaol, D= 6-Paradol, E= Trans-12-shogaol, F= Zingerone, G= Zerumbone, H= Lariciresinol, I= Gingerenone A

Table 2: Potential Targets for Selected Bioactive Components of Ginger

There would be interlinks in the biochemistry of those targets with similar possible pathogenesis. For example, ACE and CA are zinc metalloenzymes that could cause hypertension but they differ in location and reaction. All the CA targets of ginger in table 2 belonged to the cytoplasmic CA isozymes [22, 23], and not membrane bound.

CONCLUSION

Ginger could be referred to as natural therapeutic gold, due to its great potential in the treatment of multiples of human diseases. Ginger has high potential in the prevention and management of cancer, neurodegenerative dementia and cardiovascular diseases in human. Ginger components could therefore be made as pharmaceutical active ingredient either alone or in a combinatorial formulation. Further research is needed to identify possible ginger-drug interactions.

ADDITIONAL INFORMATION

The author declares no competing financial interests.

REFERENCES