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Computational evaluation of selected ginger components therapeutic potential in relevance to human diseases

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ABSTRACT

Ginger, the rhizome of the Zingiber officinale, an herbaceous tropical perennial plant belonging 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. 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.

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

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INTRODUCTION

Ginger, the rhizome of the *Zingiber officinale*, an herbaceous tropical perennial plant belonging 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 hepato-protective [4,2,5]. 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

The Ligands

Nine active ingredients of ginger were selected from the available literature [4,7,2]. 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.

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. The possible pathogenesis of each of the target was extracted from the literatures.

RESULTS AND DISCUSSION

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. The overview of the possible pathogenesis of these targets as reported in various literatures (table 3), revealed the wide therapeutic potential of ginger.

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).

Ginger component	MW	HA	AH	FC	RB	HBA	HBD	MR	TPSA	LogP	LogS	GA	LV	BS
A	294.39	21	6	0.59	10	4	2	84.55	66.76	2.76	-2.96	High	0	0.55
B	346.46	25	6	0.52	13	4	1	103.13	63.60	5.67	-4.88	High	0	0.55
C	276.37	20	6	0.47	9	3	1	82.91	46.53	3.99	-3.7	High	0	0.55
D	278.39	20	6	0.59	10	3	1	83.39	46.53	4.11	-3.72	High	0	0.55
E	360.53	26	6	0.61	15	3	1	111.75	46.53	7.24	-5.82	High	1	0.55
F	194.23	14	6	0.36	4	3	1	54.54	46.53	1.11	-1.8	High	0	0.55
G	218.33	16	0	0.53	0	1	0	70.62	17.07	3.94	-3.68	High	0	0.55
H	360.40	26	12	0.40	6	6	3	97.09	88.38	2.40	-3.53	High	0	0.55
I	356.41	26	12	0.29	9	5	2	101.49	75.99	3.74	-4.15	High	0	0.55

A= 6-Gingerol, B= 1-Dehyro-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.

Target	Target Uniprot ID	Ginger Components								
		A	B	C	D	E	F	G	H	I
5-hydroxytryptamine receptor 1A	P08908	*		*	*	*				*
5-hydroxytryptamine receptor 1B	P28222	*		*	*	*				*
Arachidonate 5- lipoxygenase	P09917	*		*	*	*			*	*
Arachidonate 12- lipoxygenase, 12Stype	P18054	*		*	*	*			*	*
Arachidonate 12- lipoxygenase, 12Rtype	O75342	*		*	*	*			*	*

Arachidonate 15- lipoxygenase	P16050	*		*	*	*			*	*
Arachidonate 15- lipoxygenase B	O15296			*	*	*			*	*
Epidermis-type lipoxygenase 3	Q9BYJ1	*		*	*	*			*	*
Carbonic anhydrase 1	P00915				*		*			
Carbonic anhydrase 2	P00918				*		*			
Carbonic anhydrase 3	P07451				*		*			
Carbonic anhydrase 5A, mitochondrial	P35218				*		*			
Carbonic anhydrase 5B, mitochondria	Q9Y2D0				*		*			
Carbonic anhydrase 7	P43166				*		*			
Carbonic anhydrase 13	Q8N1Q1				*		*			
Corticosteroid 11-betadehydrogenase isozyme 1	P28845	*								
Hydroxysteroid 11-betadehydrogenase 1- like protein	Q7Z5J1	*								
Microtubule-associated protein tau	P10636		*							
Tyrosyl -DNA phosphodiesterase 1	Q9NUW8		*							
Zinc finger protein GLI1	P08151							*		
Zinc finger protein GLI2	P10070							*		
Transcriptional repressor GLI3R	P10071							*		

*= 70-100% probability. A= 6-Gingerol, B= 1-Dehyro-10-gingerdione, C= 6-Shogaol, D= 6-Paradol, E= Trans-12-shogaol, F= Zingerone, G= Zerumbone, H= Lariciresinol, I= Gingerenone A.

Table 3: Possible Pathogenesis of the Target.

Target	**Possible Pathogenesis of the Target**	**Ref.**
5-hydroxytryptamine receptor 1A	Anxiety, Depression, Parkinson's disease, Emesis, Nausea	[10, 11, 12]
5-hydroxytryptamine receptor 1B	Hypophagia, Acute vascular constriction, Coronary artery spasm	
Arachidonate 5- lipoxygenase	Asthma, Leukemias, Solid tumors, Pulmonary arterial hypertension, Scleroderma, Arthritis, Sepsis, Atherosclerosis	[13, 14, 15, 16]
Arachidonate 12- lipoxygenase, 12Stype	Diabetes, Atherosclerosis	
Arachidonate 12- lipoxygenase, 12Rtype	Ichthyosis, Diabetes, Atherosclerosis	
Arachidonate 15- lipoxygenase	Ischemic Heart Disease, Asthma, Diabetic cardiomyopathy,	
Arachidonate 15- lipoxygenase B	Atherosclerosis, Atherothrombotic	
Epidermis-type lipoxygenase 3	Ichthyosis	
Carbonic anhydrase 1	Anaemia	[17, 18, 19]
Carbonic anhydrase 2	Glaucoma	
Carbonic anhydrase 3	Metabolic acidosis	
Carbonic anhydrase 5A, mitochondrial	Obesity	
Carbonic anhydrase 5B, mitochondria	Obesity	
Carbonic anhydrase 7	Epilepsy, Antineuropathic pain	
Carbonic anhydrase 13	Metabolic acidosis	
Corticosteroid 11-betadehydrogenase isozyme 1	Obesity, Memory impairments with aging	[20, 21]
Hydroxysteroid 11-betadehydrogenase 1- like protein		
Microtubule-associated protein tau	Alzheimer's disease, Pick disease, Down syndrome	[22, 23]
Tyrosyl -DNA phosphodiesterase 1	Erectile dysfunction, Pulmonary hypertension, Acute refractory cardiac failure	[24]
Zinc finger protein GLI1	Psoriasis, Cancer	[25, 26]
Zinc finger protein GLI2	Fibrosis, Diabetes	
Transcriptional repressor GLI3R	Cancer	

All the ginger components in this study as showed in table 1, obeyed the Lipinski rule of drug-likeness [27], which accounted for their high absorption, solubility and skin permeability. They have similar bioavailability score, which was a function of the rotation bonds [28]. 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 [27]. The ADME rules and properties accounted for drug-likeness in human, but does not predicted if a compound is pharmacologically active. Thus, 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.

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 [29], angiotensin-1 converting enzyme (ACE) and arginase in relevance to hypertension and atherosclerosis respectively [30,31], α-glucosidase in relevance to type-2 diabetes [32]. The result of these studies indicated moderate inhibition of the targets by ginger extract, which were similar to the report of Sanghal *et al.*, [33].

There are fewer works on the therapeutic potential of ginger on all of the targets in table 3, except lipoxygenases [4,34-37]. The lipoxygenases has been reported to have intimately linked activities [13]. The report of Nievergelt *et al* [34] indicated that 10-shogaol, 1-dehydro-6-gingerdione, and particularly the whole lipophilic ginger extract partially activate the 5-HT_{1A} receptor (20–60% of maximal activation). Ginger extract has been reported as an inhibitor of lipoxygenase, cycloxygenase, interlukin, and as an activator of P53 and Bax in cancer management [4].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 [18,19], 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. There is need for further computational and experimental exploration of the targets that were disclosed in this study especially the carbonic anhydrase, to ascertain the role of ginger either as an activator or inhibitor, in relevance to human diseases therapy.

ADDITIONAL INFORMATION

The author declares no competing financial interests.

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