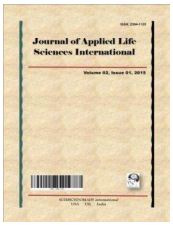

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Evaluation of Empirical Functions and Fate of Isomaltose

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Authors' contributions

This work was carried out in collaboration between all authors. Author THF designed the study, performed the computational analysis, wrote the protocol and wrote the first draft of the manuscript. Authors DMS and DUM managed the analyses of the study. Authors HUU, CJA and BCF managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To validate the empirical functions of isomaltose and proposed its fates in metabolism using computational analysis.
Place and Duration of Study: This work was carried out at the Department of Biochemistry at the Federal University of Technology Akure Nigeria in 2017.
Methodology: We make use of text mining of experimental articles on isomaltose, predicted the potential targets using *Swisstargetprediction* server, and the *Swisssimilarity* server was used for drug similarity analysis.

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Results: Isomaltose exhibits antimicrobial activity, biodegradability, non-toxic, and find its use in food, biochemistry and pharmaceutical industries as a prebiotic molecule, precursor metabolite and potent medicine respectively. Isomaltose possibly has a lower glycemic index, with the fate that implicated the production of diglucosamine, by the help of specific aminotransferase, and that there is a possibility of biosynthesis of secondary metabolites through isomaltose pathway.
Conclusion: This study provides the future areas of research and application of isomaltose.

Keywords: Isomaltose; diglucosamine; novel pathway; in silico; functions; fate.

1. INTRODUCTION

Isomaltose (6- *O*-α-*D*-glucopyranosyl-*D*-glucopyranose) is a disaccharide that comprises an alpha-1,6-glycosidic bond between two glucose molecules. Isomaltose is a member of the isomalto-oligosaccharide group, which are known to improve the general well-being of humans and animals when ingested orally daily at a moderate dose of 8-10 g, with an average of 2.8 mg availability in the urine of healthy, fasting individual [1,2,3]. Isomaltose caloric value has been found to be less than 50% that of sucrose, and its viscosity is lower than that of maltose [4]. Although isomaltose is actively hydrolysed by the disaccharidase (isomaltase) in the small intestinal mucosa, small amounts of the unhydrolyzed may be absorbed and excreted in the urine when high intestinal concentrations are attained. However, congenital sucrase-isomaltase deficiency (CSID), an autosomal recessive disaccharidase deficiency, has been recognised as the cause of isomaltose intolerance [5]. From a practical point of view, isomaltose is used as a prototype of the starch and glycogen branching, once branching in these polymers occurs through the (α-1,6) glycosidic bond between two glucose residues of the polymeric chain [6]. Surprisingly, despite the importance of the isomaltose, few published studies can be found that provide insights into its metabolic functions. In this study, functions of isomaltose are propounded and its fates in metabolism are predicted by *in silico* analysis. This study provides an advanced knowledge of isomaltose for possible industrial applications.

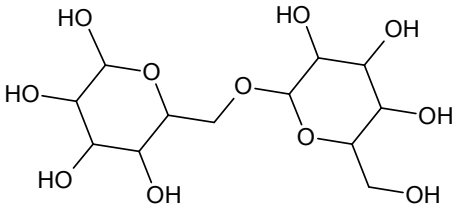

Fig. 1. Typical structure of isomaltose

2. MATERIALS AND METHODS

2.1 Text Mining of Functional Properties

The metabolic pathway in an organism where isomaltose is located was obtained from www.kegg.jp. The text mining for 'isomaltose' was done by queried PubMed database and other texts were obtained from Google search. Reports on various functions of isomaltose were intelligently mined from the available literatures, and possible scientific bases were postulated for the functions and fate of isomaltose.

2.2 In silico Target Prediction

The potential target for isomaltose and its proposed associated metabolites, were analysis using *Swisstargetprediction* server (http://www.swisstargetprediction.ch) using the SMILES (Simplified Molecular Input Line Entry Specification) obtained through Chemsketch (http://www.acdlabs.com), and *Homo sapiens* was selected as the target source [7].

2.3 Drug Similarity Search

Isomaltose and its proposed associated metabolites were compared to the available US Food and Drug Agency (FDA) approved drug database by combine screening method using *Swisssimilarity* server (http://www.swisssimilarity.ch) [8].

3. RESULTS AND DISCUSSION

At the time of this study, PubMed journal database has 564 published articles that included 'isomaltose' between the year 1949 and 2017, while only 20 of these articles make use of 'isomaltose' in their title. Also, there are 47 published articles that include 'diglucosamine', and only 1 of the articles make use of 'diglucosamine' in its title.

3.1 Isomaltose as a Prebiotic Molecule

Isomalto-oligosaccharide (IMO) is a non-digestible, low calorie health sweetener that supports the proliferation of the beneficial bacteria residing in the large intestine (colon), and consequently acts as a prebiotic [9,10]. Prebiotic is defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, that can improve the host health [11-14]. However, the degree of non-digestibility must be established. In the case of isomaltose, active hydrolysis is balanced with non-hydrolysis by glucose homeostasis which reflects the balance between the rate of glucose entering the circulation and the rate of glucose leaving the circulation.

Based on the differences observed in the glycemic index of sucrose and isomaltulose, that ingestion of slowly absorbed isomaltulose attenuated postprandial hyperglycemia by reducing oral glucose appearance by secretion of glucagon-like peptide 1 (GLP-1), inhibiting endogenous glucose production (EGP), and increasing splanchnic glucose uptake (SGU) compared with ingestion of rapidly absorbed sucrose in patients with type 2 diabetes mellitus (T2DM) [15]. It could be deduced that isomaltose will also have lower glycemic index than maltose or sucrose, in that both isomaltulose (α-*D*-glucopyranosyl-1,6-*D*-fructofuranose) and isomaltose, are catalyzed by isomaltase. Thus, isomaltose will be a low glycemic index carbohydrate.

3.2 Isomaltose as a Precursor Metabolite

Previous study has shown that natural and engineered bacteria can effectively assimilate isomaltose by implication of phospho-α-glucosidase and phosphoenolpyruvate-dependent maltose phosphotransferase system (PEP:PTS), leading to the formation of isomaltose-6-phosphate [16,17]. In *Streptomyces coelicolor*, fructose, N-acetylglucosamine, and possibly two other carbohydrates are transported by the phosphotransferase system [18,19]. This reveals possible association of isomaltose with glucosamine pathway. Different aminoglycoside antibiotics has been found and produced by few species of *Streptomyces,* which include paromomycin, trobamycin, kanamycin and framycetin (Table 2).

Glucosamine (GlucN) is one of the most commonly fermented substrates among human and animal *Bifidobacteria* [20], and numerous *Bacteroides spp.* found in the colon are known to ferment GlucN [21].

However, from a biological point of view, the presence of isomaltose has been associated with metabolic and renal illness [3,22], which include age-related macular degeneration (AMD), a leading disease that cause vision loss and blindness at old age [23]. This may be the result of inhibition of arginine:isomaltose aminotransferase (AIAT), a possible novel enzyme that catalyzes formation of diglucosamine from isomaltose. This inhibition could be the cause of high blood plasma concentrations of isomaltose and associated amino acids such as phenylalanine, tyrosine, methionine, while lower level of *N*1-Methyl-2-pyridone-5-carboxamide, biliverdin and hydrocortisone could be an indication of blockage of purine alkaloid route, and diversion to alternative route for biosynthesis of alkaloids derived from ornithine, lysine and nicotinic acid; and reduction in iron absorption, as implicated in affected metabolic pathways [23]. Previous report has shown that glucosamine sulfate inhibits tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and proinflammatory cytokine-induced production of Intercellular Adhesion Molecule 1 (ICAM-1) in human retinal pigment epithelial cells *in vitro* [24,25]. Glucosamine sulfate (GlcN-6S) is essentially beneficial in the treatment of osteoarthritis [26], and it is possibly produced from GlcN in the presence of dietary methionine [27] or from the degradation of heparitin sulfate and chondroitin sulfate by the specific glucosamine-6-*O*-sulphatase is some bacteria [28].

In addition, IMO increases the production of beneficial short-chain fatty acids such as butyrate and the absorption of calcium and magnesium [29,30], in that they serve as backbone for the formation of lipid A. Diglucosamine ($GlcN_2$) is an isomaltose-like compound formed from two units of glucosamine (2-amino-2-deoxyglucose) or by hydrolysis of chitin. The occurrence of diglucosamine (Fig. 3) has been reported present as the component of the lipid A in the membrane of some bacteria, where it played vital role in protection against environmental stresses [31,32]. No evidence of GlcN-related effects on the use of oral GlcN for individuals at risk for diabetes, or those with type 1 or 2 diabetes, or normo-glycemic with respect to any adverse

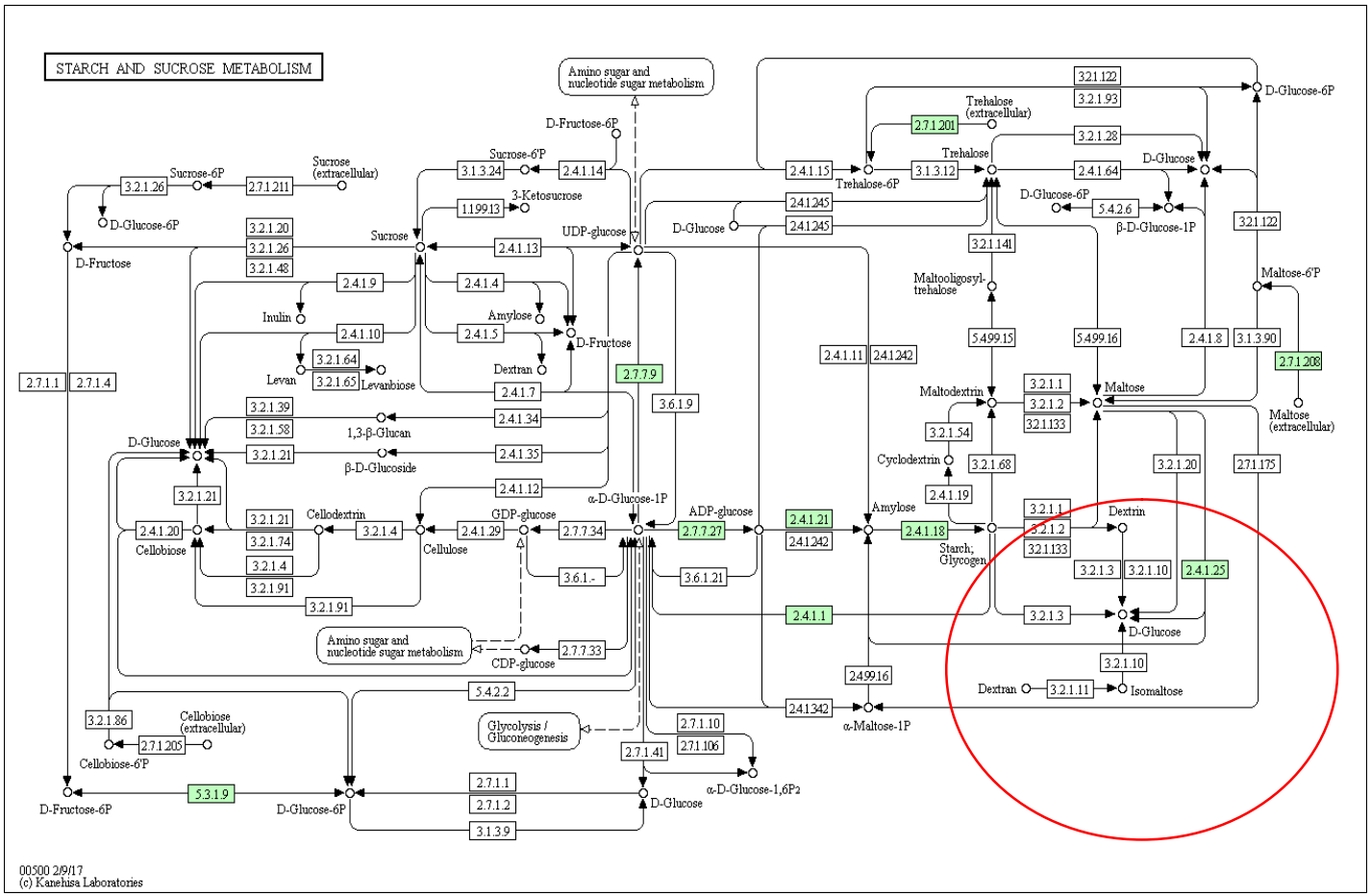

Fig. 2. Starch and sucrose metabolic pathways obtained from www.kegg.jp. Area in red shows the position of isomaltose

effects on sugar metabolism [33]. GlcN acts as a preferred substrate for the biosynthesis of glycosaminoglycan chains and subsequently to produce aggrecan and other proteoglycans of cartilage [26]. In humans, the average endogenous production of glucosamine is 12 g/day [34]. This may lead to the possible fate of isomaltose in metabolism, as it could serve as salvage pathway to the production of $GlcN_2$ and eventually GlcN, with the help of specific aminotransferase and glycoside hydrolase sequentially as shown in Fig. 4. A typical aminotransferase is found the cytosol while the glycoside hydrolase is in the lysosome.

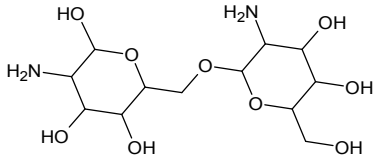

Fig. 3. Typical structure of diglucosamine

3.3 Isomaltose as a Potent Medicine

Alkyl glycosides are a group of attractive surfactants. They exhibit antimicrobial activity, biodegradability and low toxicity [35], and find their use in pharmaceutical industry [36]. Isomaltose is one of the novel alkylated halogenated disaccharides which were patented as a formulation, based on the pharmaceutical efficacy such as permeation enhancer and antimicrobial activity [37]. Study has shown that the entrapment of bovine serum albumin (BSA) into the liposomes was increased by the $GlcN_2$ [38]. Isomalto-oligosaccharides have been used for treatment of chronic constipation and hyperlipidemia occurring as complications of maintenance haemodialysis [2]. In *Aspergillus nidulans* and *Aspergillus oryzae,* study has shown that isomaltose is a physiological inducer for amylase [39,40], and that inhibition of adenylosuccinate synthase (ADSS) or a more proximal enzyme in the adenylosuccinate (S-AMP) biosynthesis pathway, adenylosuccinate lyase (ADSL), lowers S-AMP levels and impairs glucose-stimulated insulin secretion (GSIS) [41]. Also, melibiose and isomaltose, were reported as a promoter of quercetin glycoside absorption in rats by increasing glycoside hydrolysis in the intestinal lumen, and that α-1,6 linkage is involved in this process [42].

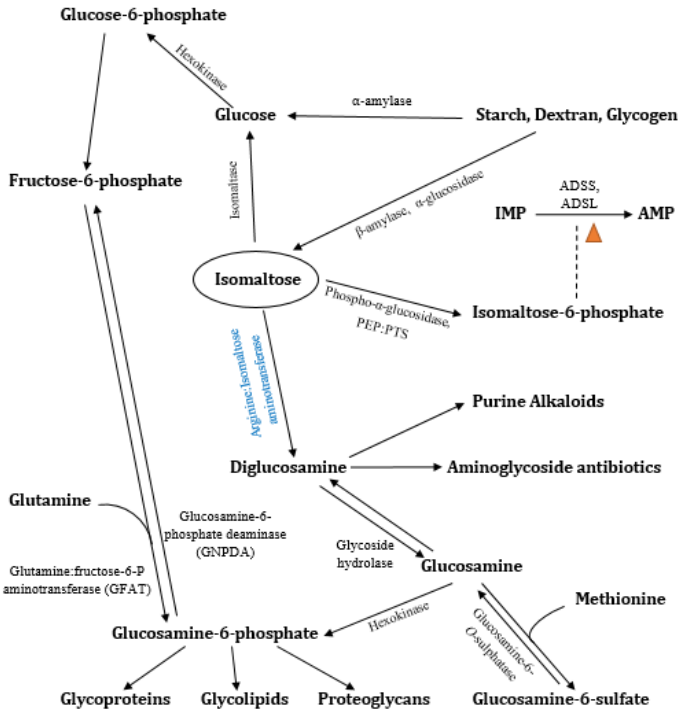

Fig. 4. Possible fate of isomaltose in metabolism. The blue colour indicates proposed enzyme (arginine:isomaltose aminotransferase) while orange colour indicates induction of adenylosuccinate synthase (ADSS) and adenylosuccinate lyase (ADSL) by isomaltose-6-phosphate

Table 1. Potential targets of isomaltose and its proposed associated metabolites

Target	Uniprot ID	Associated compounds			
		A	B	C	D
Cyclin-dependent kinase 1,2,3,4,6	P06493, P24941, Q00526, P11802, Q00534	****		**	
Fibroblast growth factor 1, 2	P05230, P09038	****		**	
Muscarinic acetylcholine receptor M1,2,3,4,5	P11229, P08172, P20309, P08173, P08912	***			
Vascular endothelial growth factor A	P15692	***			
Heparanase 8 kDa subunit	Q9Y251	**			
Inactive heparanase-2	Q8WWQ2	**			
Cation-independent mannose-6-phosphate receptor	P11717		**		*
Pyruvate kinase isozymes M1/M2	P14618		*		*
Microtubule-associated protein tau	P10636			***	
Tissue and plasma alpha-L-fucosidase	P04066, Q9BTY2			**	
Glucoamylase	O43451			*	
Sucrase	P14410			*	
Carbonic anhydrase 1, 12	P00915, O43570			*	

** (20-30%), ** (40-50%), *** (50-60%), **** (70-80%) Probability on Target. Probabilities have been computed based on a cross-validation. They may therefore not represent the actual probability of success for any new molecule.*

A = Isomaltose, C(C1C(C(C(C(O1)OCC2C(C(C(C(O2)O)O)O)O)O)O)O)O

B = Isomaltose-6-phosphate, OC1OC(COC2OC(COP(O)(O)=O)C(O)C(O)C2O)C(O)C(O)C1O

C = Diglucosamine, NC1C(O)OC(COC2OC(CO)C(O)C(O)C2N)C(O)C1O

D = Glucosamine-6-phosphate, C(C1C(C(C(C(O1)O)N)O)O)OP(=O)(O)O

Table 2. Similarity data for isomaltose and its proposed associated metabolites

FDA approved drug	Drugbank ID	Similarity score	
		Isomaltose	Diglucosamine
Kanamycin	DB01172	0.300	0.860
Paromomycin	DB01421	0.346	0.810
Lactulose	DB00581	0.994	0.754
Tobramycin	DB00684	0.159	0.679
Glucosamine	DB01296	0.205	0.605
Neomycin	DB00994	0.207	0.605
Framycetin	DB00452	0.207	0.605
Gentamycin	DB00798	-	0.267

Therefore, there is possibility of biosynthesis of secondary metabolites through isomaltose pathway (Fig. 4), especially aminoglycoside antibiotics and rare alkaloids that consist of adenine-like molecule, which could help in cellular functioning such as pathogen exocytosis, and proper protein folding by preventing aggregation [43]. It could be said that if isomaltose is an intermedia, then $GlcN_2$ will likely be an obligatory intermedia in the synthesis of specific purine alkaloid. Intermedia is a compound which can be the final product of any pathway. An obligatory intermedia is a compound which follows the intermedia in the synthesis process of the alkaloid and metabolism pathway. Moreover, inosine monophosphate (IMP) is an intermedia whenever purine is an alkaloid precursor. For non-amino acid precursor, the obligatory intermedia is derived either from intermedia by *S*-Adenosylmethionine-dependent *N*-methylation or by a coupling reaction [44].

Based on the data of Tables 1 and 2, isomaltose possibly has physiological induction property, due to its action on cyclin-dependent kinases, and fibroblast growth factor among others. These two targets are associated with heat shock protein Hsp70 and Hsp90 respectively. The highest similarity score is 1. The high similarity match of isomaltose to lactulose (a synthetic disaccharide used in the treatment of constipation and hepatic encephalopathy, as well as in the diagnosis of gastrointestinal disorders), confirmed the earlier empirical function of isomaltose [2]. Diglucosamine showed more pharmacological properties for neurodegenerative dementia such as Parkinson disease, due to its probable action on microtubule-associated protein tau. It has high similarity score to antibiotics drugs (kanamycin, paromomycin, tobramycin, neomycin, and framycetin), in addition to lactulose. This suggests the possibility of diglucosamine being a metabolically active product of isomaltose, and provide platform for synthetic development of novel drug molecules [45].

4. CONCLUSION

This study revealed the potentials of isomaltose as a material for pharmaceutical, food and biochemistry applications. The major problem initiated by this study is the occurrence of arginine: isomaltose aminotransferase (AIAT) and the pathway leading to alkaloid biosynthesis. However, there is an urgent need for further research to validate and provide biochemical solution to these problems.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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