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Research Article
An *in silico* Modeling for the Prediction of Metformin Interaction with Gadolinium-Based MR Contrast Agent

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Abstract

Background and Objective: The continued use of metformin with magnevist, a gadolinium-based MR imaging contrast agent, has been demonstrated to likely exhibit effects of antagonism and synergism. Metformin, a common drug used for the treatment of diabetes mellitus, works to lower glucose concentration in the blood and plasma. There has been a lack of consensus regarding its cessation and resumption in patients advised to undergo contrast-enhanced examinations. This predictive study was performed to elucidate the underlying drug-drug interactions (DDI) of metformin with magnevist in patients undergoing contrast-based imaging examinations. **Materials and Methods:** The possible effects of combined administration of metformin and magnevist were investigated by ChemDIS-Mixture (v.5.0, medium confidence score 0.4). The significance level for the analysis was set at 0.05, with Benjamini-Hochberg multiple test correction. **Results:** The results of the study demonstrated various proteins, gene ontology (GO), disease ontology (DO) and DOLite terms to be in common with both metformin and magnevist. The study findings revealed one GO term denoting signalling pathway (cysteine-type endopeptidase activity), five DO terms (opportunistic mycosis, essential tremor, sudden infant death syndrome, severe combined immunodeficiency and combined T cell and B cell immunodeficiency) and four DOLite terms (osteosarcoma, vascular dementia, adenoma and amyotrophic lateral sclerosis) to be new for the analysis. **Conclusion:** The use of metformin in patients scheduled for contrast-based imaging examinations should be considered by radiologists and medical doctors and the drug interactions between metformin and magnevist should be deeply studied before their combined use in patients.

Key words: Magnetic resonance imaging, magnevist, metformin, drug-drug interaction, toxic effects, ChemDIS-Mixture, malignant

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Throughout their lifespan, human beings are intentionally and non-intentionally exposed to various chemicals which could prove to be beneficial and malignant for their health. This exposure is not limited to one chemical at a time, as multiple chemicals can work in tandem which can result in health complications. Over the years, scientists have worked on ways to facilitate the prediction of one chemical on the human body, whereas less research has been done to computationally elucidate the effects of multiple chemicals on the body at a single time, thus rendering the latter to be desirable under certain circumstances. In comparison to direct interactions of one chemical with another, the determination and understanding of potential indirect interaction of two chemicals which collectively cause a disturbance in routine biological pathways remains to be an ambiguous feat. For achieving this, many computational techniques and software have been developed, such as ChemDIS, a chemo-genomics software that establishes an understanding of various proteins, functions and biological pathways affected by the interaction of two chemicals with each other. Therefore, this software is significant for the integrative analysis and the identification of possible end-points of co-exposure generated from the interaction of two or more chemicals[1].

Metformin is a biguanide and extensively indicated to reduce the post-prandial and basal level of plasma glucose in type 2 diabetes mellitus patients. This hypoglycemic agent acts through the suppression of both hepatic glucose production and intestinal glucose absorption. A major part of metformin is excreted without undergoing metabolism[2]. Its half-life is 5 hrs. It has extensive physiological distribution after oral intake[3]. Metformin uptake from renal epithelium cells is enabled by OCT2, encoded by the *SLC22A2* gene expressed at the basolateral membrane in the renal cells. The excretion of metformin is regulated by MATE-1 and MATE2-K, encoded by *SLC47A1* and *SLC47A2* genes, respectively[4]. Both proteins are expressed in the renal tubule membranes (apical part) which have been reported to positively regulate the excretion of metformin in healthy patients[5].

The cessation and presumption of metformin have been surrounded in controversy for patients who have been scheduled to undergo phase-contrast imaging examinations. The Canadian Association of Radiologists (CAR) advise the cessation of metformin administration before examination in patients who have an approximate rate of glomerular filtration (eGFR) to be <60 mL min^{-1}, while the European Society of Urogenital Radiology (ESUR) believes that a patient scheduled for imaging examination should stop taking metformin at least 48 hrs before the test, is the patient has an eGFR rate[6] <45 mL min^{-1}.

This study aimed to predict the possible drug interaction of metformin with magnevist, a gadolinium-based Magnetic Resonance Imaging (MRI) contrast agent, as well as the biological pathways, diseases and related genes that were affected by the interaction of both drugs. This predictive *in silico* study employed the use of ChemDIS-Mixture, a significant online tool for computational analyses that predict the potential interactions between two or multiple drugs, thereby identifying the associated molecular pathways, proteins, gene and diseases ontologies that are disrupted or involved due to the interactions of these drugs in the human body.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Radiology, Wuhan Fourth Hospital, China from January to June, 2021).

Criteria for analysis: ChemDIS-Mixture is an online database that has two versions of the same software available online (4.0 and 5.0, respectively). The latest version (v.5.0) is an updated version of the former and is significant for the prediction of drug interactions as it is enabled to sequester data from more databases for various drugs and chemicals. Similar to the STITCH database, three different levels of confidence score are defined at ChemDIS-Mixture as well (low-0.15, medium-0.4 and high-0.7, respectively) (Fig. 1)[1]. The predictive interaction of metformin with magnevist was studied by adopting a systematic method, as depicted in Fig. 2. The name of each drug was added (Fig. 1) into the search bar of the database, followed by adjusting the parameters as a hypergeometric test (Benjamini-Hochberg multiple test correction adjusted to $p<0.05$) for enrichment analysis of GO, DO, DOLite terms and the associated signalling pathways.

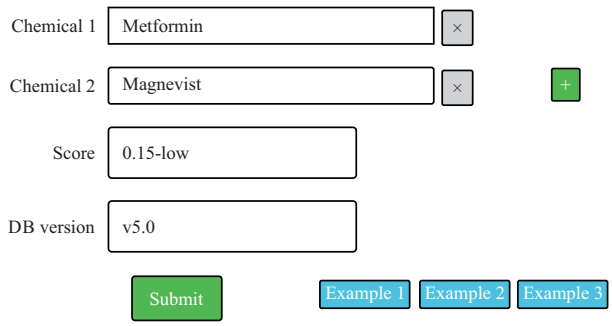

Fig. 1: Metformin and magnevist were written as the input chemical 1 and chemical 2 in the given slots
ChemDIS-Mixture can study the interaction among four chemicals at a time. "Score" represents confidence score, which could be high, medium or low. For this study, medium type score (i.e., 0.4) was utilized

Findings of analysis: ChemDIS-Mixture is an online tool with vast data of chemicals, drugs and their compounds, which has been sequestered from other databases such as PubChem. Moreover, the tool itself contains a wide variety of target proteins and their 2-D as well as 3-D structures, also fetched from other databases. Therefore, the analyses and their outputs performed via this tool are depicted in the form of various target proteins and their associated signalling pathways, GO, DO, DOLite terms which are then represented on Microsoft® Excel® and as mathematical Venn diagrams for depicting the drug-drug interactions (DDI).

RESULTS

A schematic representation of the interaction of metformin with magnevist predicted via ChemDIS-Mixture has been shown in Fig. 2. Venn diagrams are presented in Fig. 3, which were based on the associated proteins, GO, DO, DOLite terms as well as the signalling pathways. The computational analysis also yielded some hyperlinked terms which were then downloaded and tabulated in Microsoft Excel®.

Proteins: Metformin with magnevist is linked with 633 and 62 proteins, respectively. The results of the analysis demonstrated 14 proteins to be associated with both drugs and 709 overall effects generated in the human body through the co-administration of metformin with magnevist (Fig. 3a). Both metformin and magnevist have an association with cytochrome P450 enzymes (CYP450). CYP2C11, CYP2D1 and CYP3A1 metabolized both metformin and magnevist, which reveals the possibility of pharmacokinetic intervention when both agents are co-administered. This condition may lead to a delayed elimination of MRI agents or metformin toxicity.

Signalling pathways and GO terms: The analysis showed the co-administration of metformin with magnevist to generate 103 shared GO terms (Fig. 3b), as compared to 1101 and 178 GO terms of metformin and magnevist, respectively. Moreover, one new GO term was reported in the study, with 187 overall effects. The new GO term obtained as a result of metformin-magnevist co-prescription (unique in overall effect) was cysteine-type endopeptidase activity (GO:0004197). Adj. P1, Adj. P2 and Adj. Point values were 6/675, 55/16309 and 0.02552, respectively. It revealed the significant likeliness of cysteine-type endopeptidase activity on concomitant use of metformin and magnevist in comparison with propranolol use alone. Furthermore, the co-administration of metformin with magnevist yielded 306 SMPs for metformin and 57 SMPs for magnevist (Fig. 3c), while 21 SMPs were similar in both drugs. Overall effects were 67.

DO terms: The analysis presented 522 and 40 DO terms for metformin and magnevist, respectively, while the shared DO terms were 303 (Fig. 3d). Overall effects were reported to be 823, with five new DO terms generated, known as

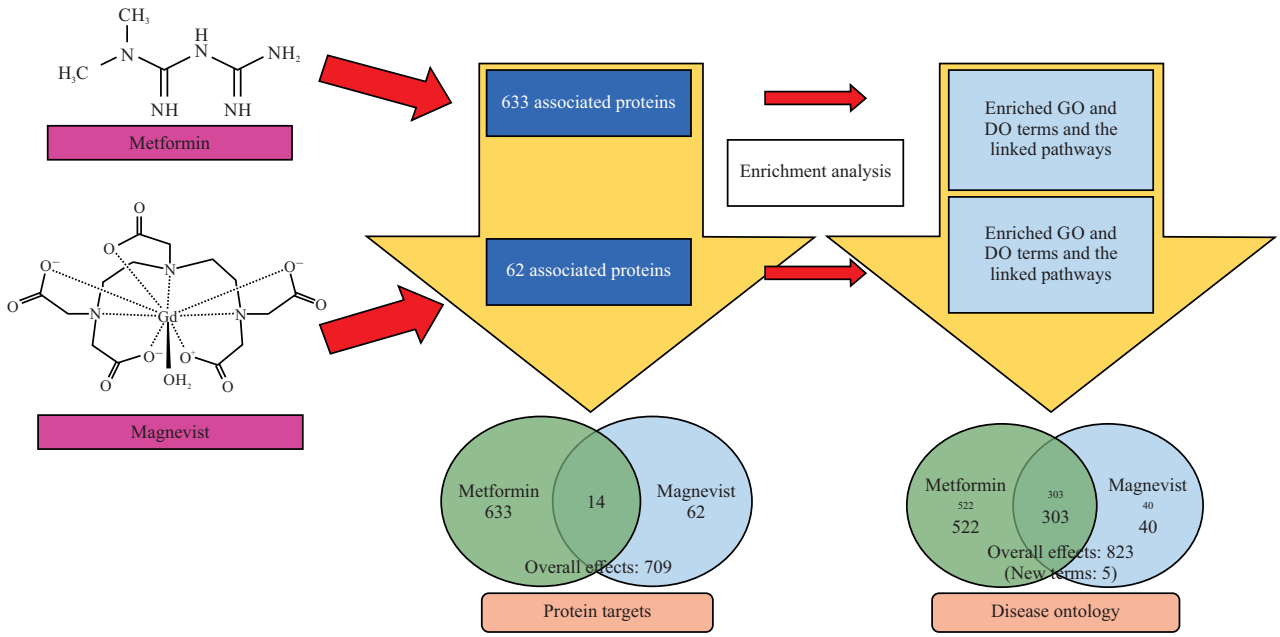

Fig. 2: A diagrammatic representation of magnevist interaction with metformin studied through ChemDIS-Mixture

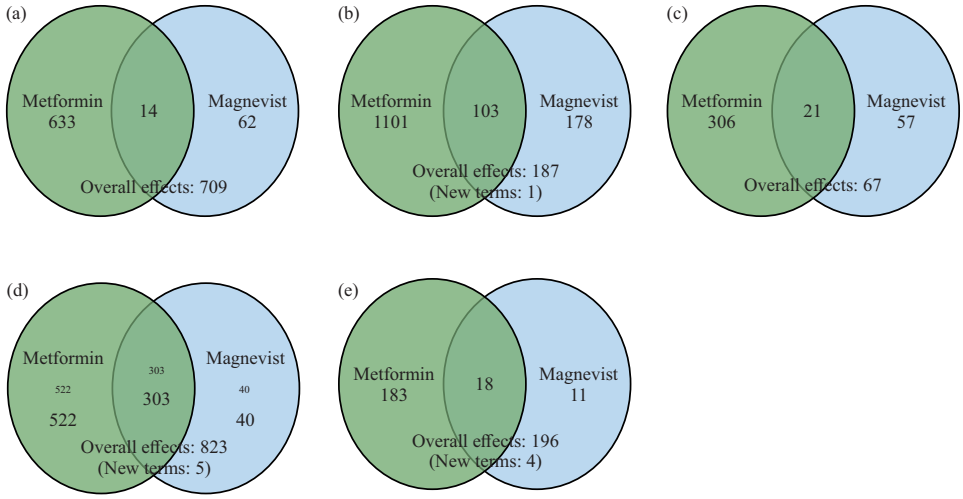

Fig. 3(a-e): Metformin-magnevist interaction in Venn diagrams based on the associated, (a) Proteins, (b) GO, (c) Signalling pathway, (d) DO and (e) DOLite terms

Table 1: New DO terms obtained as a result of metformin-magnevist co-prescription (unique in overall effect)

DOLite ID	Description	Gene ratio	Bg ratio	p-value	Adj. P	Genes
DOID:2473	Opportunistic mycosis	6/499	39/8007	0.03211	0.03533	TGFB1, PLG, p38ALPHA, IL1B, BSF-2
DOID:4990	Essential tremor	4/499	20/8007	0.03252	0.03550	SNCA, SLC6A3, GBA, CYP2C9
DOID:9007	Sudden infant death syndrome	4/499	20/8007	0.03252	0.03550	BSF-2, SCA-1, IL10, 5-HT-1A
DOID:627	Severe combined immunodeficiency	7/499	50/8007	0.03408	0.03652	CD34, TNLG6B, DPP4, FOXN1, MYC
DOID:628	Combined T cell and B cell immunodeficiency	7/499	52/8007	0.04107	0.04295	CD34, TNLG6B, DPP4, FOXN1, MYC

Table 2: New DOLites obtained as a result of metformin-magnevist co-prescription (unique in overall effect)

DOLite ID	Description	Gene ratio	Bg ratio	p-value	Adj. P	Genes
DOLite:400	Osteosarcoma	5/301	22/4051	0.02016	0.02454	NR1I2, ENX2, IGF1, ACTSA, CXCL8
DOLite:547	Vascular dementia	3/301	9/4051	0.02436	0.02808	HEL-S-21, LDLCQ5, DCP1
DOLite:31	Adenoma	6/301	34/4051	0.03667	0.03971	SELENOP, MODY10, GPR182, BSF-2, AGTR1...
DOLite:48	Amyotrophic lateral sclerosis	8/301	55/4051	0.04820	0.04844	SCA-1, CLGI, CCL2, p38ALPHA, 5-HT-1A...

opportunistic mycosis, essential tremor, sudden infant death syndrome, severe combined immunodeficiency and combined T cell and B cell immunodeficiency (Table 1). Based on the findings, gene ratio 4-7 out of 499 genes and Bg ratio 20-52 out of 8007 are associated with these disease ontologies. GeneRatio resembles M/N. Here, M is the geneset size of the annotated distribution input list and resembles the signalling pathways. While N represents the size of all sole genes in the collection of genesets. Similarly, BgRatio is similar to A/B where B reflects all genes in the database. The database of the acquired signalling pathway terms has a specific number of genes. P- and Adj. p-values for all DOLite terms were less than 0.05, revealing that a significantly higher number of genes have linkage with the pathogenesis of the tabulated diseases (Table 1) on co-administration of metformin and Magnevist. Even So, the use of metformin alone identifies a nonsignificantly ($p<0.05$) the low number of disease ontologies, likely due to malfunctioning of different genes including interleukins, cytochrome P450 and solute carrier proteins.

DOLite: The analysis of metformin and magnevist produced 183 and 11 terms for metformin and magnevist, respectively, whereas the number of shared DOLite terms was 18 (Fig. 3e). Overall effects produced were 196, of which four new effects were revealed to be osteosarcoma, vascular dementia, adenoma and amyotrophic lateral sclerosis (Table 2). This tabular data show that the retrieved DOLite disease ontologies have a gene ratio of 3-8 out of 301 genes and Bg ratio of 9-55 out of 4051. Here p-values and Adj. p-values for all these terms is less than 0.05. These findings show that a significantly large number of genes play a vital role in the pathogenesis of the tabulated diseases (Table 2) on simultaneous administration of metformin and magnevist and the occurrence of these disorders (mainly cancer) is comparatively low ($p>0.05$) than metformin alone.

DISCUSSION

Living beings are complex, intricate systems that interact with a whole other lot of sub-systems which are then functional for countless known and unknown biological functions, pathways and processes, respectively. Therefore, when a disease is inflicted on the body, these systems and their sub-systems tend to malfunction in a way that affects the immune system of the body, a complex phenomenon. Consequently, the treatment of these diseases should always be contingent on those chemicals and drugs which positively interact with the body, thereby aiming to aid in treating the disease on the whole, rather than just looking at one aspect of the disease. This is one of the main reasons drugs are used singularly or in combination with other drugs. However, some drugs tend to interact with one another when they are given in combination or without stopping the first drug, which can lead to drug-drug interaction (DDI)[7]. Diabetes mellitus is a disease that causes metabolic disorders in the body, marked by hyperglycemia caused by an inadequate supply of insulin in the body. It is divided into four major types, i.e., type-1 diabetes, type-2 diabetes, gestational and monogenic diabetes, respectively. Type-1 patients need to inject insulin due to the destruction of pancreatic β cells[8]. However, patients with type-2 diabetes are prescribed metformin, one of the most common drugs taken orally for lowering the blood glucose level in diabetic patients. As metformin is not metabolized in the human body, it is excreted in its unchanged form via the kidneys which can ultimately affect the pharmacokinetics of the drug[9]. Previously, it was thought that due to the drug being not metabolized it can therefore not be involved in many DDIs, which led to the notion that variegation in the pharmacokinetic nature of the drug was attributable to the genetic mutations in the transporters of the drug, giving way to the fact that DDIs of metformin with other drugs is more significant than previously thought[10]. It is commonly known that patients with type-2 diabetes also are inflicted with other comorbidities for which they are described other medications. Therefore, pharmacokinetic variations by other drugs can cause a wide array of side effects, such as lactic acidosis, a well-known complication of taking metformin along with other drugs[11].

In this study, the predictive analysis of co-administering metformin along with magnevist, a gadolinium-based contrast imaging agent was investigated. The results of the study depicted one new GO term, cysteine-type endopeptidase activity (GO ID: 0004197). Cysteine proteases belong to the five major classes of enzymes (proteolytic), which aid in the hydrolysis of peptide bonds[12]. The characteristic feature of cysteine proteases is the cysteine residue being present at the active site of the enzyme[13]. The DO term analysis yielded five new terms, known as opportunistic mycosis (DOID:2473), essential tremor (DOID:4990), sudden infant death syndrome (DOID:9007), severe combined immunodeficiency (DOID:627) and combined T cell and B cell immunodeficiency (DOID:628). Patients with combined T cell and B cell immunodeficiency are inflicted with re-current infections that are presented early, with increased susceptibility to many infections and diseases, which may or may not be treatable by immunotherapy. Severe Combined Immunodeficiency Disease (SCID) is the most aggressive form of immunodeficiency disorder, which may be diagnosed early in life or could arise late in life. In this diseased condition, both B and T cell abilities are hindered or completely non-functional which results in the patient being severely immunodeficient[14]. If diagnosed early, the condition may be treatable for the prevention of susceptible infections. But in cases of late diagnosis, the lifespan of the patient may be reduced significantly[15]. Many of the cases tend to have an underlying cause of variation among immune cells, which is also important when classifying the type of SCID affecting the patient, typically assessed by the absence of B or T cells or both[16]. This absence can be characterized by the genes which ultimately are responsible for the presence and absence of B and T cells, as observed from the mutations in the T cells which consequently lead to the inhibition of B cells in producing specific antibodies[17]. This type of immunodeficiency disorder is observed to associate with the co-prescription of metformin and magnevist, as demonstrated by our study.

The DOLite term analysis revealed the presence of four new terms, namely, osteosarcoma (DOLite:400), vascular dementia (DOLite:547), adenoma (DOLite:31) and amyotrophic lateral sclerosis (DOLite:48). The occurrence of dementia has been reported to increase remarkably in the world, which can also be related to several other co-morbidities such as diabetes, cardiovascular disease and an overall decline in health with increasing age. Previous studies have reported the incidence of type-2 diabetes in more than 15 % of dementia patients[18], which is why diabetes is reported to be majorly associated with cognitive impairment and decline[19], but the reasons for it are not elucidated clearly. Many factors such as poorly regulated blood sugar levels, damage to blood vessels over time, as well as the presence of other co-morbid factors are one of the many reasons type-2 diabetes is closely associated with or is thought to aid in the progression of dementia[20,21].

While ChemDIS-Mixture is an online tool and offers a prediction of the possible drug-drug interactions between two or more drugs, validation is always needed in the form of *in vitro* or *in vivo* studies, which can aid greatly in authenticating the *in silico* prediction which is offered by this software.

CONCLUSION

Metformin is a drug that is prescribed worldwide for the non-insulin therapy of diabetes mellitus. Although this drug is not metabolized in the body, its uses can yield various side effects in the body if an underlying medical factor or secondary health condition is involved. Moreover, as observed from this predictive analysis, the co-administration of metformin with magnevist, a gadolinium-based MR imaging contrast agent can produce several effects in the human body, some of which can tend to be toxic if both are taken together. Hence, it is necessary to carefully monitor the prescription of metformin and the case history of the patient undergoing contrast-based imaging examination, as well as the dosage concentration.

SIGNIFICANCE STATEMENT

This study predicted the interaction of gadolinium-based MR imaging contrast agent with metformin that can be beneficial for healthcare providers. This study will help the researchers to uncover the critical areas of drug-diagnostics interaction that many researchers were not able to explore. Thus a new theory on drug-diagnostics interaction may have arrived at the suggestion of a guideline on careful MRI scans of metformin-treated patients.

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