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Research Article

Integrative Investigation and Prioritization of Candidate Genes *PTGS-2* and *VEGF*: Unveiling their Interaction with Celecoxib for Targeted Therapeutic Applications

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Abstract

There is a huge amount of data available on genes interacting with celecoxib in terms of drug response; however, these studies are inconsistent in outcomes. To overcome this inconsistency, there is a significant need to integrate the available data and categorize genes interacting with celecoxib. We conducted the extraction of data from published articles (n=30511) with reference to celecoxib-gene interactions from online literature sources, using a semi-automated text mining approach. Moreover, scoring algorithms were developed by assigning each gene a score depending on the available evidence according to Coriell Personalized Medicine Collaborative Pharmacogenomics Appraisal evidence scoring systems. We generated prioritized gene sets based on evidence scores; subsequently, twenty-seven genes with evidence were identified to be associated with the response to celecoxib from the literature search. Seven genes were found to affect clinical outcomes of celecoxib, whereas, thirteen genes were found associated with pharmacodynamics (PD) and pharmacokinetics (PK), and seven genes were identified with potential clinical relevance. Our analysis revealed that individuals with an increased expression of *PTGS-2* and Vascular endothelial growth factor (*VEGF)* genes respond better to celecoxib. Thus, we utilized a semi-automated machine learning approach to extract genes from a wide-ranging corpus of scientific literature and prioritized a set of twenty-seven genes based on the consistency and strength of evidence. Furthermore, these identified genes can be used for validation and replication in multiethnic cohorts and animal models to evaluate the response variation to celecoxib.

Keywords: Genetic polymorphism, *PTGS-2*, *VEGF*, celecoxib, gene-drug interaction, genome-wide association studies

1. Introduction

There are numerous non-steroidal anti-inflammatory drugs (NSAIDs) available worldwide to treat inflammation, relieve pain, and reduce fever (Domiati and Ghoneim 2015). The anti-inflammatory and pain-relieving effects of NSAIDs resulted from the inhibition of prostaglandin (PGs) synthesis mediated by cyclooxygenase 2 (COX-2) enzyme (Graham 2006). Celecoxib is the first selective COX-2 inhibitor NSAID approved for clinical practice (Davies et al. 2000). Celecoxib is fundamentally recognized as benzene sulphonamide, which belongs to diaryl-substituted pyrazole compound structurally known as 4-[5-(4-methyl phenyl)-3-trifluoromethyl-1H-pyrazoyl-1-yl]

(Rao and Knaus 2008). It is specified by FDA for the treatment of acute pain, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and familial adenomatous polyposis (FAP), and adenomatous colorectal polyps (Gong et al. 2012). Furthermore, celecoxib has also exhibited potential in cancer prevention and has been used as an adjunctive in surgery in patients with FAP, the hereditary colon cancer susceptibility syndrome, to minimize the number of adenomatous colorectal polyps (Gong et al. 2012).

Its actions take effect by inhibiting COX-2 isoenzyme specifically, with 30-fold more selectivity, than COX-1 enzyme; however, it minimally inhibits COX-1 only at therapeutics concentration (Gong et al. 2012), resulting in the inhibition of prostaglandin-endoperoxide synthase 2 (PGH2) synthesis. This is a crucial step for PGH2 production from arachidonic acid, catalyzed by COX enzymes (PTGS1, and PTGS2). Active metabolites obtained by conversion of PGH2s are prostacyclin (PGI2), thromboxane (TXA2), prostaglandin D2 (PGD2), prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2), which result in various physiological responses as fever, inflammation, pain, regulation of blood pressure, and clotting (Bruno, Tacconelli, and Patrignani 2014). Expression of *PTGS2*/*COX-2* is normally insignificant but it could be induced by cytokines, the stress in several tissues, and growth factors. In inflammatory diseases, the level of PTGS2 is increased, such as in arthritis. The exact mechanism of the anti-cancer effect shown by celecoxib remains unclear, but it probably involves both COX-dependent and COX independent mechanisms (Chiang et al. 2017). The antineoplastic mechanisms of celecoxib usually involve the regulation of angiogenesis, induction of apoptosis, and cell cycle arrest. Apoptosis induction by celecoxib seems to be associated with pro-apoptosis molecule-activation such as caspases, along with the inhibition of antiapoptotic molecules. Furthermore, celecoxib-mediated blockage of cell-cycle progression has been seen in experiments of cell culture, in addition to upregulated expression of cell cycle inhibitors. Celecoxib therapy decreases the Vascular endothelial growth factor (*VEGF)* expression and causes the matrix metalloproteinase 9 inhibition (*MMP9)* in cell lines, and cancer tissues (Sobolewski et al. 2010).

It is known that genetic polymorphisms showed a significant susceptibility to metabolic enzyme expression, drug receptors, transporters, and inter-individual variation-associated influences on PD or PK profiles of drugs (Phan et al. 2011). A wide range of genetic variations can affect drug PK, which results in altered efficacy, and toxicity of pharmaceutical agents (Wyatt et al. 2012). Earlier studies have shown a relation between inter-individual variation in *COX-2* gene expression and variability in responses (Lee et al. 2017). Genetic polymorphisms in different populations may lead to noteworthy individual variations in several drugs, resulting in serious ADRs or treatment failures (Li et al. 2018). Extensive Individual-to-individual variability in responses to COX-inhibiting drugs limits their clinical efficacy and safety. The adverse outcomes associated with cardiovascular events of selective COX-2 inhibitors have caused drug withdrawal from the market by the Food and Drug Administration (FDA). In 2005, the FDA placed a black-box warning on celecoxib (Pirlamarla and Bond 2016) following the reports of elevated risk of cardiovascular and gastrointestinal events adverse events after celecoxib use (Pfizer 2019). Similarly, long-term treatment with celecoxib has been found to increase the risk of cardiovascular, like myocardial infarction and coronary death (Brænne et al. 2017).

Heritability studies indicate that the interpersonal variation in *COX-2* gene (*PTGS2*) expression could alter individual responses to celecoxib. According to previous studies, variability in response to celecoxib was 30%

Table 1. Evidence code assignment for gene-Celecoxib interaction.

Evidence Code Definition			
Evidence Score	**Study Category**	**Study Objectives/Findings**	**Assessment of Outcomes**
1	Clinical outcome studies	*Consistent effect of a genetic variant on a drug of interest	Clinically relevant
2	PK or PD Study	*Consistent effect of a genetic variant on a drug of interest	Clinically relevant
3	Molecular or Cellular functional studies	*Consistent effect of a genetic variant on a drug of interest	Potential clinical relevance
4	Clinical outcome studies	Inconsistent effect on the drug of interest	Clinical relevance unknown
5	PK or PD Study	Inconsistent effect on the drug of interest	Clinical relevance unknown
6	Molecular or Cellular functional studies	Inconsistent effect on the drug of interest	Clinical relevance unknown
7	Clinical outcome studies, PK or PD study	Demonstrates no effect of the genetic variant on drug response	Clinical relevance unsupported

PD: Pharmacodynamics, **PK:** Pharmacokinetics.

collectively in COX-1 and COX-2 enzymes; moreover, approximately 6.8% of cardiovascular events were reported in patients of osteoarthritis, and rheumatoid arthritis receiving celecoxib therapy (Fries et al. 2006, Pfizer 2019). However, the FDA Arthritis Advisory Committee has recommended that the label should state that 0.2% with celecoxib, and 1.7% with other NSAIDs; serious upper GI adverse event rates might be expected (Davies et al. 2000).

Pharmacogenetics and pharmacogenomics (PGx) studies have assessed the genomic basis of the variability of response in individuals on celecoxib therapy. There are a number of genes identified to be associated with inconsistent drug response, and adverse drug reactions to celecoxib. There are various reasons for the failure of the implementation of personalized medication therapy of celecoxib, such as the lack of multiethnic pharmacogenetic data for making accurate clinical decisions. According to ethnic and racial background, the occurrence of specific alleles differs amongst different populations. This has an influence on side effect profiles and dosing regimens in different ethnicities, globally (Stamer, Zhang, and Stuber 2010). Well-equipped metacentric trials in which patients with a well-defined phenotype are enrolled and study for several genes are needed. In genetic association studies patients' history, drugs administered, and social and psychological factors are represented as very important confounders (Stamer, Zhang, and Stuber 2010). There is a severe dearth of consistency and integration, of a huge amount of data on gene-celecoxib interaction in terms of drug response.

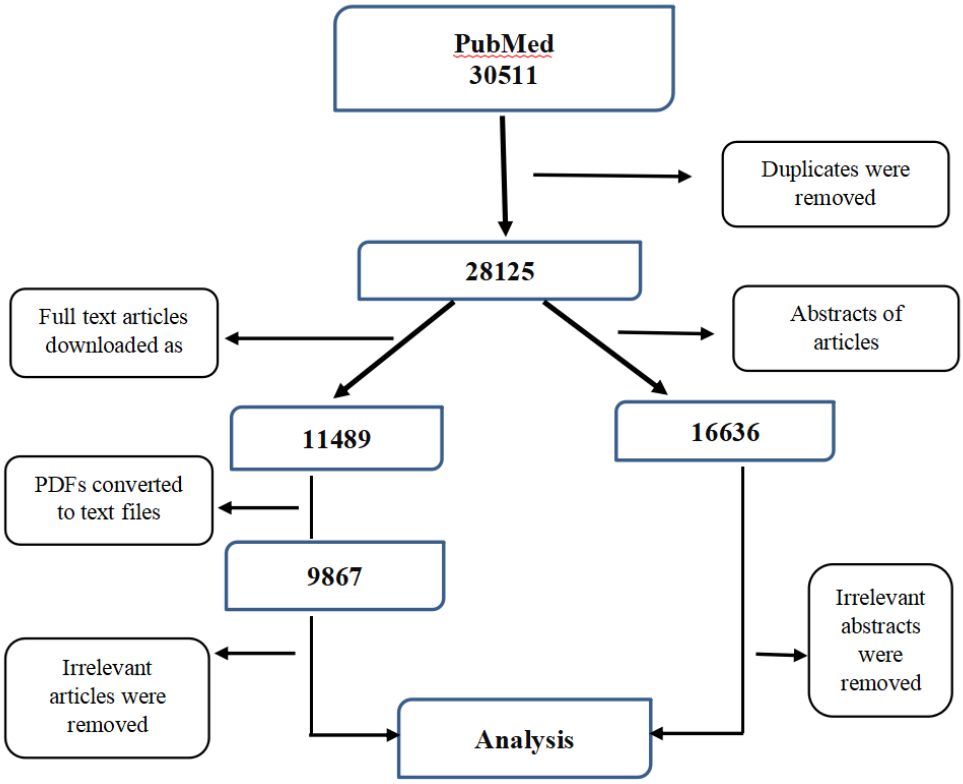

Figure 1. Flowchart of selection and extraction of articles

Given the extensive literature on gene–celecoxib interactions, obtaining an impartial overview of evidence poses a considerable challenge. That is why this study aimed not just to compile data and understand genes affecting celecoxib response but also to outline its adverse effects, considering the strength of available data. For this purpose, a semi-automated text mining approach was applied to overcome the inconsistency of available data and to collect evidence. Cataloging this evidence to prioritize candidate genes and identifying relevant genetic biomarkers among prioritized genes for further assessment is essential. There is a necessity to evaluate the role of PGx in personalized celecoxib therapy. This evaluation will contribute to comprehending gene–celecoxib interactions and facilitate the future utilization of celecoxib in precision medicine.

2. Materials & Methods

2.1. Candidate Drug Selection

The candidate drug selection is based on a number of criteria mentioned in the Pharmacogenomics Appraisal, Evidence Scoring and Interpretation System (PhAESIS) study (Gharani et al. 2013). According to PhAESIS study, the drug selection criteria are as follows:

a) The drug must be included in the FDA label (Pharmacogenomic Biomarkers in Drug Labels Table).
b) International or national drug usage statistics (DrugStats 2019, Pharmacy-Times 2018).
c) Inclusion of drug in Indiana University School of Medicine Cytochrome P450 table of drug interaction.
d) The description of the drug must be present in scientific or clinical publications

or in relevant databases of Pharmacogenomics, as mentioned in Pharmacogenomics Knowledgebase (PharmGKB).

e) Clinically significant variable drug response in terms of impact and severity (e.g. a result of genetic variance related to a serious adverse drug reaction or the FDA drug label with a particular 'black box' warning) (Pfizer 2019).

f) The drug that shows potential effects that can modify prescribing pattern (alternative therapy or dosing) or which require more frequent monitoring, to enhance efficacy and minimize the risk of severe adverse reactions.

Celecoxib was selected for the current study, as it met all of the above-mentioned parameters for pharmacogenomics research appraisal.

2.2. Data Collection and Cleaning

2.2.1. Selection and screening of Articles

PubMed® or Medline® and Scopus databases were used to search out related articles with reference to celecoxib and genes. Literature searches on PubMed were done with the terms that include, (a) Celecoxib and Celebrex (name of drug) AND "pharmacogenetics OR pharmacogenomics", (b) individual genetic variants of the relevant gene and/or "star nomenclature" of PGx (Gharani et al. 2013). In a single notepad file, the PMIDs (PubMed articles identifiers) of relevant articles were collected from the database (PubMed) and used for automated download and retrieval of full-text articles with the help of Endnote and/or Batch Entrez. The articles were downloaded in PDF format and were converted to text files by using an available PDF converter (Nitro Pro 9).

2.3. Gene, and Drug Dictionary Development

2.3.1. Gene Dictionary

In biomedical literature, a wide range of naming conventions, synonyms, and conducts of writing for genes have been reported. Gene dictionary construction was done using different resources, namely Gene Cards, Google, NCBI gene, Symatlas, and the University of California, Santa Cruz (UCSC) genome browsers.

2.3.2. Drug Dictionary

Much like genes, drugs also adhere to a naming convention. Alternative names of celecoxib are used in different articles; hence, we created a drug dictionary to capture extensive data from the literature. Thus, a drug dictionary was developed containing brand names, generic names, and International Union of Pure and Applied Chemistry (IUPAC) names, along with synonyms, aiding in extracting valuable information from biomedical literature. This drug dictionary for celecoxib was implemented using drug cards available in DrugBank.

2.4. Sentence Segmentation and Tokenization Process

After the collection of sentences, the process of sentence segmentation and their tokenization was done. To collect information from a bulk of biomedical literature, an important step was to split a string of texts into its components by specifying sentence boundary detection. Sentence segmentation is a process of recognizing the boundaries of sentences in the text of an article. Python programming software along with its Natural Language Toolkit (NLTK) package was required for the segmentation of sentences. In tokenization, the sequence of characters is broken up in the text with the addition of word boundaries (Palmer 2000). This process was done by adding white spaces and punctuation. After the addition of these spaces, each segmented word was considered as a token.

2.4.1. Name Entity Recognition (NER) with the Terms of Drug and Genes Dictionaries

Name Entity Recognition (NER) is a process of tracing and sorting names in a text. In this context, NER was employed to extract information, specifically names related to celecoxib, genes, and their synonyms, using constructed gene and drug dictionaries. Utilizing Python-based algorithms and software with built-in functions, along with the NLTK

Table 2. Genes with evidence of annotation and impact along with frequencies.

Genes	Evidence										
	Annotation		Sub-Annotation						Impact		Frequency
	DE	IE	A	HI	DI	dI	Spec	N	CR	GE	
PTGS-2	498	66	449	61	17	10	16	11	544	20	564
STAT3	11	7	15	0	3	0	0	0	18	0	18
p53	3	6	5	0	3	0	0	1	7	2	9
ESR1	4	15	10	1	3	3	2	0	19	0	19
PIK3CA	0	5	5	0	0	0	0	0	5	0	5
HER-2	1	4	1	1	0	0	2	1	5	0	5
CYP2C9	123	14	111	5	10	4	4	3	136	1	137
CYP3A4	1	3	3	0	1	0	0	0	4	0	4
CYP2D6	5	0	1	0	4	0	0	0	5	0	5
PGHS-2	120	10	110	11	9	0	0	0	128	2	130
EGFR	10	14	6	4	12	1	1	0	22	2	24
AKT	11	28	13	3	17	0	6	0	37	2	39
UGT1A1	0	3	2	0	0	0	1	0	3	0	3
CDH11	4	2	4	0	1	1	0	0	4	2	6
PI3K	4	4	3	0	5	0	0	0	8	0	8
MMP9	0	4	0	4	0	0	0	0	4	0	4
BCL-2	0	10	0	0	0	10	0	0	10	0	10
GADD153	0	5	4	1	0	0	0	0	5	0	5
IL-1β	3	14	3	1	8	3	2	0	17	0	17
VEGF	16	22	11	5	17	1	3	1	27	11	38
IL-6	0	3	0	0	0	3	0	0	3	0	3
MTOR	0	3	0	1	2	0	0	0	1	2	3
CRP	0	6	0	0	4	1	1	0	0	6	6
IL-12β	0	3	0	0	0	3	0	0	0	3	3
MRP4	7	3	2	5	0	1	2	0	10	0	10
MDR1	1	3	1	0	3	0	0	0	1	3	4
IFN-γ	1	0	0	0	0	0	1	0	0	1	1
Wnt-β	0	1	1	0	0	0	0	0	1	0	1

IE: Indirect Explicit, **DE:** Direct Explicit, **DI:** Direct explicit, **A:** Amplified Interaction, **N:** Unknown, **HI:** Hypothetical Interaction, **Spec:** Speculation, **Neg:** Negation, **dI:** Direct inferred, **PK:** Pharmacokinetics, **PD:** Pharmacodynamics, **CR**: Clinical Relevance, **CI:** Clinical Irrelevance

data package, entities were tagged with specific labels. Sentences, with the name of the drug and a gene, were extracted from each article along with the titles of the articles. To handle any ambiguity, PMIDs, and titles were appended to each extracted sentence for reference. A unique number was assigned to each sentence for the purpose of identification.

2.5. Annotation of Extracted Sentences

Every single sentence was manually annotated to establish the relationship between celecoxib and genes, following the annotation guidelines outlined by the Gene-Drug Interaction Corpus and Comparative Evaluation mentioned in the DIEGO lab (http://diego.asu.edu/). This evaluation was based on an assumption that drug-gene pairs were frequently clustered together in a sentence. The effect of the gene/drug on the expression of the protein was determined by identifying the gene that encodes the specific protein. This effect was assumed to be elucidated with interaction words; such words provide evidence about the presence of an interaction. Interaction words, such as 'action', 'influence', or 'effect' refer to the effect of the gene on the pharmacodynamics, pharmacokinetics, and clinical outcomes of the drug. Additionally, the influence, action, or effect of a drug on gene expression was also included in the interaction. Each sentence must contain at least one interaction word to be considered for annotation.

2.5.1. Main Annotation Categories

The annotations used for confirming the presence or absence of an interaction between a drug and genes are the primary annotations. These can be direct annotations or indirect and inferred or explicit interactions.

2.5.1.1. Direct and Indirect

Direct interaction refers to the absence of intermediary entities, as a part that is needed for a comprehensive understanding of the interaction. Entities were important for a full semantic understanding of the interactions that were connected to both the drug and the gene or either of the two; they are regarded as intermediary entities. The sentence was to be annotated under "indirect effect" in the presence of any intermediary entity.

2.5.1.2. Explicit and Inferred

Explicitness is attributed to the text that unambiguously expressed the gene-drug interaction; whereas the interaction was referred to as "inferred" when the interaction is from ambiguous text. Thus, for the current analysis regarding annotation of interactions, three categories of data i.e., direct explicit interactions and/or indirect explicit and/or indirect inferred interactions were considered and documented. For further analysis, direct explicit interaction was to be studied.

2.5.2. Annotation Subcategories

Several annotation subcategories were used if they exist in sentences along with interactions. These included decreased interaction, amplified/affirmative interaction, hypothetical interaction or speculation, difficult inference, and negation.

A 'decreased interaction' is indicated by the decline in the interaction between a gene and a drug. Whereas, an 'amplified interaction' exhibits a positively increased interaction between the gene and the drug. The hypothetical interaction is an assumed interaction between a gene and a drug in the previous or present analysis. Another term under the subcategory is known as 'difficult inference' in which it is tough to identify the interaction among entities. In contrast to decreased interaction, negation means the absence of interaction and is commonly stated as 'never', 'not', and other negative words. Speculation is described by words as 'might' or 'possibly' in a text. Statements with difficult inferences and speculative interactions were not significant enough to be annotated for this study.

2.6. Developing an Evidence Scoring Algorithm

The scoring algorithm was developed based on the relevance, consistency, and frequency of co-

Table 3. Genes associated with clinical outcomes of celecoxib

Genes Affecting Clinical Outcome with Annotation and Scoring

Genes	Annotation	Sub-Annotation	Impact	Effect	Evidence Score
PTGS-2	DE	A	CR	C	1
STAT3	DE	A	CR	C	1
p53	IE	A	CR	C	1
ESR1	IE	HI	CR	C	1
PIK3CA	IE	A	CR	C	1
HER-2	IE	Spec	CR	C	1
MRP4	DE	HI	CR	C	1

DE: Direct Explicit, **IE:** Indirect Explicit, **A:** Amplified Interaction, **HI:** Hypothetical Interaction, **Spec:** Speculation, **DI:** Decreased Interaction, **C:** Clinical Outcome, **CR:** Clinical Relevance.

occurring gene and celecoxib pairs in PGx. The algorithm assigned scores to each gene based on the available evidence of their interaction with celecoxib (Gharani et al. 2013). Genes were assigned scores ranging from 1 to 7, where a score of 1 represented the strongest evidence (indicating a significant clinical impact), and a score of 7 represented the weakest evidence (suggesting minimal or no effect of gene-drug interaction on drug response).

The term 'consistency' in the scoring mechanism refers to the enhancement of the effect of genes and drugs on each other, producing the same effect at least twice. For example, if there is evidence supporting the drug producing an effect on the gene and/or the gene on the drug, and two instances contradict the action, the effect would be deemed consistent, regardless of a decrease or increase in drug response. For instance, if 500 sources of evidence in the corpus state, "the clinical outcome enhanced by certain gene" and 300 out of the evidence oppose the statement, we would conclude that the clinical outcomes consistently increased by that gene, as the evidence supports this conclusion outweighs the contradicting evidence.

The scoring algorithm table was developed by following the scoring guidelines provided by (Gharani et al. 2013). Studies were categorized into three different groups: Type I clinical outcomes studies considered the greatest level of PGx evidence, followed by type II PK and PD studies, and type III molecular and cellular functional studies with decreased and lowest evidence.

2.6.1. Clinical Outcome Studies

The change in clinical outcomes, such as morbidity, mortality, side effects, and the cure rate, is described by clinical outcomes studies. Those studies demonstrate a significant change in therapeutic outcomes attributed to genetic variants in the response to drugs. This category of studies may encompass clinical trials, case-control studies, case series, cohort studies, as well as case reports.

2.6.2. Pharmacokinetics (PK) and Pharmaco-dynamics (PD) Studies

These studies aim to observe the effect of genetic variants on absorption, distribution, metabolism

Table 4. Genes associated with pharmacokinetics of celecoxib.

Genes Affecting Pharmacokinetics with Annotation and Scoring

Genes	Annotation	Sub-Annotation	Impact	Effect	Scoring
CYP2C9	DE	A	CR	PK	2
CYP3A4	IE	A	CR	PK	2
CYP2D6	DE	DI	CR	PK	2

DE: Direct Explicit, **IE:** Indirect Explicit, **A:** Affirmative, **DI:** Decreased Interaction, **CR:** Clinical Relevance, **PK:** Pharmacokinetics

and elimination (PK) of the therapeutic agent. In PK studies, genetic variants are associated with the concentration or level of the drug and active metabolites of a drug at the site of action. The studies in which genetic variants are examined in the drug targets show a significant difference in a biomarker's response to the drug. These studies, whether ex-vivo and/or in-vivo, evaluate responses related to PK and PD. They may include case-control studies, cohort studies, clinical trials, case series as well as case reports.

III) Cellular and Molecular Functional Studies: Such studies evaluate how a genetic variant changes the enzyme or protein function and cellular functions through in-vitro functional assays. For example, studies determine the variant's effect on gene activation, its expressions, enzyme kinetics, or variation of certain cellular properties in the drug response.

After collecting evidence for all the genetic variants from articles, each gene was assigned a single score based on the strength of available evidence accordingly. A significant interaction of gene-drug was assigned a score range of 1-3; whereas the score ranges from 4-6 was awarded to inconsistent or weak interactions. Lastly, score 7 was assigned to the genes for which the clinical relevancy was not present. **Table 1** shows the evidence code assignments based on the strength of available evidence for gene-drug interactions.

3. Results

3.1 Data Retrieval and Extraction

A total of 30,511 articles were identified by using celecoxib and related terms. After the removal of duplicate articles, 28,125 articles proceeded for further evaluation. Among these, 11,489 were downloaded as full-text articles, while the remaining 16,636 were downloaded as abstracts and directly exported to a notepad file from Endnote. After removing irrelevant articles, the analysis was performed. ***Figure 1*** illustrates a flowchart of the selection and extraction of articles.

Abstracts and full-text articles came from 2478, and 1741 different journals respectively. All full-text downloaded articles were converted from PDF to plain text files (txt.) using the Nitro Pro 9 PDF converter. The converted articles of text format were further analyzed in Python 3.7.4 software provided with drug and gene dictionaries of celecoxib. Both drug and gene dictionaries were constructed by extracting drug and gene names, as well as their synonyms from Drug Bank, Gene Cards, Symatlas, NCBI, USCS, and Google.

The process of extracting sentences along with their segmentation and tokenization was performed by Python software with its NLTK

Table 5. Genes affecting PK or PD of celecoxib with annotation and evidence score

Genes Affecting PK/PD with Annotation and Scoring

Genes	Annotation	Sub-Annotation	Impact	Effect	Scoring
PGHS-2	DE	A	CR	PD	2
EGFR	IE	DI	CR	PD	2
STAT3	DE	DI	CR	PD	2
AKT	IE	DI	CR	PD	2
UGT1A1	IE	A	CR	PK/PD	2
CDH11	DE	A	CR	PK/PD	2
PI3K	IE	DI	CR	PK/PD	2
MMP9	DE	HI	CR	PK/PD	2
BCL-2	IE	dI	CR	PK/PD	2
GADD153	IE	A	CR	PK/PD	2
IL-1β	IE	Spec	CR	PK/PD	2
VEGF	IE	DI	CR	PK/PD	2
IL-6	IE	dI	CR	PK/PD	2

IE: Indirect Explicit, **DE:** Direct Explicit, **DI:** Decreased Interaction, **A:** Amplified Interaction, **HI:** Hypothetical Interaction, **N:** Unknown, **dI:** Direct inferred, **Spec:** Speculation, **Neg:** Negation, **PK:** Pharmacokinetics, **PD:** Pharmacodynamics, **CR**: Clinical Relevance, **CI:** Clinical Irrelevance.

package. The drug and gene dictionaries were saved in 'csv.' format that was allowed to be read by Python NLTK. The total number of sentences extracted was 2884 (2576 from full-text articles and 308 from abstracts). After removing unwanted and irrelevant sentences, we had 1081 sentences (909 from full-text articles and 172 from abstracts) for further evaluation. These sentences were annotated for celecoxib-gene interaction and according to the annotation and scoring system, each gene was assigned an evidence score. A total of twenty-eight genes were identified from relevant articles that are responsible for celecoxib response directly or indirectly. **Table 2** shows genes with their annotation and frequencies.

3.2. Genes Associated with Relevant Clinical Outcomes of Celecoxib

We identified seven genes that alter the clinical outcome of Celecoxib and showed consistent interaction with celecoxib. The genes in this category were assigned with a score "1" and showed clinical relevancy. Under this category, the *PTGS-2* gene was found to strongly affect clinical outcomes of celecoxib with 564 numbers of evidence. COX-2 enzyme, encoded by the gene *PTGS2*, was found to alter celecoxib response with 449 affirmative evidence, whereas 17 evidence showed decreased interaction. On the other hand, *STAT3* and *MRP4* also directly affect the response of drugs with 18 and 10 total numbers of evidence, respectively. *HER-2* (human epidermal growth factor receptor 2)

showed indirect explicit interactions with a total of 5 evidences and *ESR1* (Estrogen Receptor 1) was found in the literature with 19 evidences, out of which 10 were affirmative and 3 were of decreased interaction. Also, affirmative interaction with 5 evidence for both genes *p53* and *PIK3CA* genes was found to improve the clinical outcome of celecoxib. **Table 3** shows the list of genes identified that are associated with the clinical outcomes of celecoxib.

3.3. Genes Affecting PK and PD of Celecoxib

Genes associated with PD, metabolism, and clearance of celecoxib were identified. The members of the cytochrome P450 family; CYP3A4 (Cytochrome P450 family 3 subfamily A member 4), CYP2C9 (Cytochrome P450 family 2 subfamily C member 9), and CYP2D6 (Cytochrome P450 family 2 subfamily D member 6) were found to be associated with the metabolism of celecoxib. CYP2C9, CYP3A4, and CYP2D6 with evidences 137, 4, and 5, respectively, were found to affect the PK of celecoxib. CYP2C9 has affirmative interaction with 111 evidences, and 10 evidences showed decreased interaction with the drug. CYP3A4 was annotated indirect explicit with 3 evidences, and affirmative interaction was shown by 3 evidences. CYP2D6 was a gene also associated with the Pk of celecoxib showing direct explicit and decreased interaction with 5 and 4 evidences, respectively. **Table 4** shows the genes along with annotations that are affecting the PK of celecoxib.

We have also identified 13 genes that affect the PD of celecoxib. These genes include *PGHS-2* with 130 evidences annotated direct explicit with 120 evidences and showing affirmative interaction with 110 evidences. *EGFR* (epidermal growth factor receptor) gene was found with 24 evidences, showing indirect explicit and decreased interaction with 14, and 12 evidences, respectively. *STAT3* (signal transducer and activator of transcription 3) was found with 18 evidences. *AKT* and *UGT1A1* were annotated as indirect explicit with 28 and 3 evidences, respectively. *AKT* showed decreased interaction and *UGT1A1* showed affirmative interaction with 17 and 2 evidences, respectively. *CDH11* was found with total 6 evidences annotated direct explicit with affirmative interaction 4 evidences each. *PI3K* had 8 total evidences. *MMP9* and *BCL-2* were identified as indirect explicit with 4 and 10 evidences, respectively. *GADD153*, *VEGF*, and *IL-1β* were found with 5, 38, and 17 evidences respectively, and annotated indirect explicit with 5, 22, and 14 evidences. *VEGF* was identified to decrease drug-gene interaction supported by 17 evidences. *IL-6* (Interleukin-6) and *IL-1β* (Interleukin-1 beta) showed hypothetical interactions because data in the literature did not support these interactions every time. **Table 5** shows genes that are associated with the PD effect of celecoxib along with annotations and evidence score.

The above-mentioned genes were identified as responsible for affecting the PK and PD of celecoxib based on the evidence provided in biological literature. As these identified genes were not found to consistently affect the clinical outcomes of the relevant drug, they were assigned an evidence score of "2".

3.4. Genes Associated with Potential Clinical Relevance of Celecoxib

Identified genes were found to have consistent interaction, potentially causing clinical effects of celecoxib. Genes included in this category were *MTOR*, *CRP* (C-reactive protein), *IL-12β* (Interleukin 12 beta), *CYP2C8* (Cytochrome P450 family 2 sub-family C member 8), *MDR1* (multi-drug resistance 1), *IFN-γ* (Interferon-gamma), and *Wnt-β*. Celecoxib may affect cellular and molecular functions of the above-mentioned genes that encode proteins, and these genes were assigned with an evidence score "3" because they might have potential clinical relevance.

MTOR gene (total 3 evidences) was annotated as indirect explicit (3 evidences) and sub-annotated as decreased interaction (2 evidences) have

Table 6. Genes with potential clinical relevance of celecoxib

Genes Associated with Potential Clinical Relevance of Drug

Genes	Annotation	Sub-Annotation	Impact	Effect	Score
MTOR	IE	DI	GE	M	3
CRP	IE	DI	GE	M	3
IL-12β	IE	dI	GE	M	3
CYP2C8	IE	Spec	GE	M	3
MDR1	IE	DI	GE	M	3
IFN-γ	DE	Spec	GE	M	3
Wnt-β	IE	A	CR	M	3

IE: Indirect Explicit, **DE:** Direct Explicit, **DI:** Direct explicit, **A:** Amplified Interaction, **N:** Unknown, **HI:** Hypothetical Interaction, **Spec:** Speculation, **Neg:** Negation, **dI:** Direct inferred, **PK:** Pharmacokinetics, **PD:** Pharmacodynamics, **CR:** Clinical Relevance, **GE:** Gene Expression, **M:** Molecular effect

recognized to state the clinical relevance of celecoxib with the impact of gene expression (2 evidences). *CRP* was found to have a total of 6 evidences with indirect explicit (6 evidences) annotation and decreased interaction (4 evidences). *IL-12β* gene is annotated as indirect explicit with 3 evidences and its sub-annotation category is direct inferred (3 evidences) in which the interaction of gene and drug is hard to identify. *MDR1* with a total of 4 evidences was found to affect the action of celecoxib and annotated as indirect explicit with 3 evidences, decreased interaction with 3 evidences, and found to have potential clinical relevance. *CYP2C8*, *IFN-γ*, and *Wnt-β* were also found to have an association with celecoxib, although with the lowest number of evidence reported. The number of evidence for *IFN-γ* and *Wnt-β* was much lower that is 1 for each. *Wnt-β* was annotated as indirect explicit and affirmative interaction with celecoxib, whereas *IFN-γ* was annotated as direct explicit, and the sub-annotation category was speculation. **Table 6** shows genes that are associated with the potential clinical relevance of celecoxib.

4. Discussion

Current drug development practices aim to find drug therapy suitable for an individual. Drug-gene interactions are well-defined in scientific literature, while there is a lack of description of the exact mechanisms of these gene-drug interactions in comprehensive databases. Several genes were reported to affect drug response and adverse effects and to be associated with the PGx of a drug. Hence, it is necessary to compile PGx data for a personalized treatment approach.

Previous studies show that patients differ greatly in response, adverse effects, and optimal dosage receiving celecoxib therapy. This response variability, estimated at 30%, is due to genetic and non-genetic factors. Understanding how the genetic factors impact response to celecoxib and may help in selecting individuals at risk for adverse events, might improve treatment profiles. There is vast literature present that explains drug-gene interactions, but the specific mechanism of these interactions is either not concisely described or is hard to refine. However, in the present study, we

identified genes interacting with celecoxib that affect PK/PD or clinical outcomes and have potential clinical relevance by using a semi-automated text-mining approach.

In our analysis, the drug and gene dictionaries for celecoxib were constructed, which were then used in 'Python 3.7.4' software along with text files of downloaded articles and abstracts to extract sentences from the bulk of scientific literature comprising drug and gene pairs. The sentences extracted were later annotated according to the criteria mentioned. Overall, 27 genes were identified in the current study, that interact with celecoxib directly or indirectly, showing affirmative or decreased interaction. These genes were prioritized on the basis of frequency, relatedness, and consistency of interaction with celecoxib.

We identified seven genes associated with clinical outcomes of celecoxib. The second gene set confirmed the consistency of fourteen genes that were affecting PK/PD of celecoxib without being consistently associated with clinical outcomes. Several genes were found to be clinically relevant that affect the expression and activation of genes in celecoxib presence. Furthermore, we scored these gene sets on the basis of available evidence. The top-prioritized genes were assigned score "1" which was associated with clinical outcomes of celecoxib, including *PTGS-2*, *p53*, *HER-2*, *ESR1*, *STAT3*, *PIK3CA*, and *MRP4*. The second gene set associated with PK/PD was scored "2" were *CYP2C9*, *CYP3A4*, *CYP2D6*, *AKT*, *EGFR*, *UGT1A1*, *CDH11*, *PI3K*, *MMP9*, *BCL-2*, *GADD153*, *IL-1β*, *VEGF*, and *IL-6*. And third set of genes was assigned evidence score "3" as they seemed to be potentially clinically relevant including genes *MDR1*, *MTOR*, *CRP*, *CYP2C8*, *IFN-γ*, *IL-12β*, and *Wnt-β*.

Genes with substantial evidence indicating changes in clinical outcomes or PK/PD were identified, showcasing altered cellular and molecular functions. Notably, this includes *PTGS-2* and *VEGF*. *PTGS-2* gene that encodes COX-2 enzyme, an enzyme involved in PGs production. PGs, connected with different intracellular pathways, play an important role in the process of inflammation, mediating fever, cell proliferation, tumor invasion, and cell death. Celecoxib was found to have strong evidence for anti-inflammatory, antipyretic, anti-neoplastic, and analgesic properties by inhibition of *PTGS-2* gene expression (Gong et al. 2012, Alexanian and Sorokin 2017). Celecoxib removes a physical restraint on mediators that are COX-2 mediated cardioprotective PGs, predominantly PGI2 and PGE2, that increase blood pressure, induce thrombosis, and promote atherogenesis (Grosser 2006, Grosser, Fries, and FitzGerald 2006, Vardeny and Solomon 2008, Mukherjee 2002). COX-2 inhibition in long-term treatment may produce a pro-thrombotic state and patients may be predisposed to a high risk of cardiovascular diseases (Grosser, Yu, and FitzGerald 2010). However, Harris et al. explained that there is no association between daily celecoxib use and thrombotic cardiovascular disease when a meta-analysis of 72 studies was done (Harris 2009). The *COX-2*-1195G > A (rs689466) genotype has been related to elevated gastrointestinal tumor risk, including colorectal cancer (Tomitão et al. 2017). The *VEGFA* gene is important for angiogenesis, vasculogenesis, and vascular maintenance. Its inhibition leads to hypertension. It leads to the activation of multiple downstream signaling cascades and promotes endothelial cell proliferation, migration, and tube formation relevant to angiogenesis. VEGFR2-dependent activation of PI3K-AKT-mTOR signaling regulates cell survival, cell proliferation, and anti-apoptotic and cell permeability functions in cancer cells. Celecoxib is reported to suppress the expression of *VEGFA*. However, the major single nucleotide polymorphism (SNP) at the *VEGFA* loci showed multiple associations with coronary risk factors further upholding its role in coronary artery disease have been reported in patients with higher levels of VEGF. For

genome-wide significance, the SNPs of *VEGFA* that rs6905288 also reached the well-known genome-wide association studies threshold (Brænne et al. 2017).

Our analysis found that the pharmacokinetic profile of celecoxib is dependent on *CYP2C9*, *CYP3A4*, and *CYP2D6* genes which encode CYP2C9, CYP3A4, and CYP2D6 enzymes respectively, are members of Cytochrome P450 family. Celecoxib is principally metabolized by CYP2C9, while CYP3A4 also shows a minor role by metabolizing the drug less than 25% (Davies et al. 2000, Sandberg et al. 2002, Paulson et al. 2000). Celecoxib is found to be an inhibitor of CYP2D6 metabolizing enzyme (Werner et al. 2003). As the metabolism of celecoxib is principally facilitated by *CYP2C9*, *CYP2C9* genetic polymorphisms are likely to produce a direct influence on PK and variance in drug responses. CYP2C9 substrate (CYP2C9*3 allele carrier) poor metabolizers, on comparison with usual CYP2C9 activity, have shown increased exposure to celecoxib (Kirchheiner et al. 2003, Sandberg et al. 2002, Tang et al. 2001).

We determined gene sets that included genes that showed consistent changes in therapeutic outcomes in the presence of celecoxib. The important genes *PTGS-2* and *VEGF* play an important role in the anti-inflammatory and anti-neoplastic properties of celecoxib. Celecoxib suppresses the expression of these genes and is found to produce therapeutic effects. Although the present study has produced novel evidence of gene-celecoxib interactions, it is challenging to overview complete relevant literature. For instance, the conversion of the original PDF file into text format might have caused the loss of significant data, as some articles used formats that were incompatible with the file patterns used in our study. Moreover, data confined to tables and figures in the papers were difficult to interpret in a semi-structured format. Some abbreviations that were not recognized by any protocol might lead to data loss. Such as in some articles abbreviations used for celecoxib instead of its generic or brand name (such as CXB) are used rarely, and some genes are reported to be in a nonstandard form that may not be analyzed by dictionary-based NER.

Overall, PGx profiling may be represented as a source for health professionals, leading to improved clinical care quality together with improved economic benefits for both public health and pharmaceutical industries (Mendrinou et al. 2017). Our identified gene sets derived from clinical outcomes, PK/PD, and cellular and molecular studies, including *PTGS-2* and *VEGF* genes, related to celecoxib response using a semi-automated text mining approach of the published literature. The association of genetic variation in these genes needs further validation and follow-up. Based on the robustness of PGx literature, genes linked to the pharmacodynamics/pharmacokinetics of the drug will undoubtedly offer advanced and valuable evidence, aiding in the treatment of individuals and contributing to the advancement of precision medicine. However, large studies in different population validation and conscious interpretation of PGx data are needed before it would apply to patients.

5. Conclusions

In the current study, we advanced the selection of celecoxib for various disease states by identifying a set of twenty-seven genes using a semi-automated text-mining approach. We cataloged the evidence to annotate and prioritize candidate genes that showed a definite interaction with celecoxib. Our findings specified that the gene encoding the COX-2 enzyme, *PTGS-2*, has the strongest association in mediating clinical response. Additionally, influencing the therapeutic outcomes of celecoxib included *p53, HER-2, ESR1, STAT3, PIK3CA,* and *MRP4*. Moreover, genes associated with the PK of celecoxib were *CYP2C9*, *CYP3A4*, and *CYP2D6* and among them, genetic polymorphisms of *CYP2C9* contributed to the

major PK variation of celecoxib. Thirteen genes were found affecting PD of celecoxib, whereas the genes associated with potential clinical relevance were *MDR1*, *MTOR*, *CRP*, *CYP2C8*, *IFN-γ*, *IL-12β*, and *Wnt-β*. Furthermore, text mining of the relevant published literature, we have recognized genes (PTGS-2 and VEGF) associated with celecoxib response from cellular and molecular function studies. It is critically important to validate the association of these genes in various large-scale cohort studies and extensive animal models before applying them to clinical practice. Moreover, testing for validation and/or replication of these candidate genes in multiethnic and well-powered cohorts is important. Furthermore, SNPs-level annotation and genetic risk score of these genes in various human populations will aid a step forward and will help the health policymakers to shift treatment from empirical therapy to more personalized celecoxib therapy.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA.

Authors Contribution

NS & MM conceptualized the study, A, AJS, and MIA helped in the literature review and analysis, ZU and MI helped write the first draft, A did the experimental analysis, and NS supervised the whole project and wrote the final manuscript.

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