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Research Article

A Relational Database Design for The Compounds Cytotoxically Active on Breast Cancer Cells

Zeynep OKTAY[1], Çiğdem SELÇUKCAN EROL[2,3], Nazlı ARDA[4,5]
[1]Corresponding Author; Institute of Graduate Studies in Science, Istanbul University, Turkey;
zeynepoktay2012@ogr.iu.edu.tr
[2]Department of Botany in Department of Biology, Faculty of Science, Istanbul University, Turkey
[3]Department of Informatics, Istanbul University, Turkey;
cigdems@istanbul.edu.tr
[4]Department of Molecular Biology and Genetics, Faculty of Science, Istanbul University, Turkey
[5]Center for Research and Practice in Biotechnology and Genetic Engineering, Istanbul University, Turkey;
narda@istanbul.edu.tr

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Abstract

Breast cancer is one of the most important global health problems affecting both developed and developing countries. The identification of anticancer compounds, effective on breast cancer cells, is of key importance in chemoprevention investigations and drug development studies. In the literature, there are numerous compounds that have been analyzed for their cytotoxic effects on breast cancer cells, but there is no database where the researchers who want to design a new study on breast cancer can find these compounds all at once. This paper presents a relational database that stores the data of natural and synthetic compounds cytotoxically active on breast cancer cells. The database contains 381 cytotoxicity results and data of 159 compounds, compiled from selected 80 studies. When all this data in our database was queried, it was found out that quercetin, which is a dietary flavonoid, is the most analyzed compound, and MCF-7 cell line is the most used breast cancer cell line.

Keywords: relational database, relational model, breast cancer, cytotoxic compounds, cytotoxicity analyses

1. Introduction

Female breast cancer is the most diagnosed cancer worldwide [1]. In 2020, female breast cancer with 2.26 million new cases had an 11.7% rate in other cancer types [2]. Chemotherapeutic drugs used in treatment also damage normal (healthy) cells and cause serious side effects [3]. In addition, when drug resistance to chemotherapy occurs [4, 5], the treatment becomes ineffective.

In this regard, studies are progressing to find new compounds effective in inhibiting the growth of breast cancer cells. In the scientific literature, there is a wide range of cell culture studies (*in vitro* studies) analyzing the cytotoxic effects and anticancer activities of natural and synthetic compounds on breast cancer cell lines. Especially, plant secondary metabolites, mainly flavonoids, are at the center of these studies [6, 7, 8]. Plant extracts [9], synthetic derivatives of natural compounds [10], and compounds derived from different organisms, such as fungal taxol isolated from *Pestalotiopsis pauciseta* VM1 [11] and propolis as a honeybee product [12], are the other examples of focus of these cell culture studies. The identification of compounds with cytotoxic effects is crucial to both define compounds with therapeutic potential and to provide the basis for advanced studies.

As in numerous fields, in life sciences, data has critical importance and an effect on directing the decision-making process. Databases are computerized systems used for storing, accessing, retrieving, and managing data. The relational database management system (RDBMS) is the most used database technology today. RDBMS is based on Edgar F. Codd's "relational data model" [13]. SQL, MS SQL Server, IBM DB2, ORACLE, My-SQL, and Microsoft Access are based on RDBMS [14]. The main principle in RDBMS is to store the data in the form of relations. In the RDBMS, data is stored in tables where each record is held in a row and each attribute of the data is held in a column [15, 16]. The

advantages of relational databases are the ease of adding, inserting, updating, deleting data, and practicability in data retrieval, querying, and reporting [17].

In the present study, we designed a relational database compiling natural and synthetic compounds with cytotoxic effects on breast cancer cells. We aimed this database to be the first example of a digital library of literature that presents the whole data related to those compounds in the context of compound name, publication to which it belongs, breast cancer cell line, the origin organism of the compound, the class of the compound, dose, treatment time, and cytotoxicity level for the researchers who study on breast cancer.

2. Material and Method

2.1. Literature Search and Study Selection

Schoolar Google and Science Direct databases were searched for cell culture studies assessing the effects of natural and synthetic compounds on breast cancer cell lines. Having cytotoxicity analysis results and % inhibition data were the criteria for selecting studies that would be included in our database. In selecting studies, the date range was not taken into account.

2.2. The Scope of Literature Review and General Characteristics of The Selected Studies

When we reviewed the literature by using the expressions of "breast cancer and natural compounds", "breast cancer and synthetic compounds", "breast cancer and cytotoxicity", "breast cancer and *in vitro* assays" as keywords, we came across two main group of studies with different specifications. We found that while the vast majority of studies focused solely on the cytotoxic effects of compounds (such as quercetin, lycopene, curcumin, apigenin, etc.), the other group of studies focused on the cytotoxic effects of herbal extracts. For instance, in [18] Takeshima et al. investigated the effect of lycopene, which is a plant pigment called carotenoid mostly found in tomatoes, in breast cancer cells, and in [19] Duo et al. investigated quercetin's effect. On the other hand, in [20] Alsabah et al. studied the effects of *Xanthium strumarium*, which is an annual herb, against breast cancer cell lines.

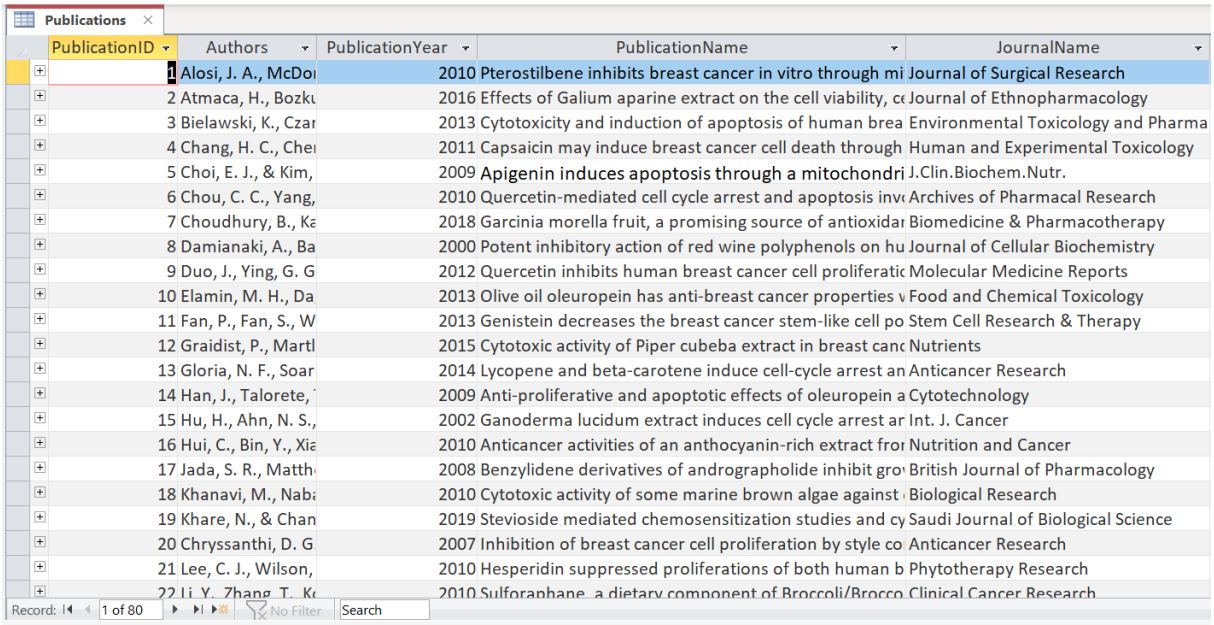
In our literature review, we also saw multi-component studies that assess more than one compound's cytotoxic effect on more than one breast cancer cell line. For instance, in [21] Ligresti et al. investigated the antitumor activity of five different plant cannabinoids (cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC acid) on two different breast cancer cell lines (MCF-7 and MDA-MB-231 cell lines). In [22] the authors investigated the cytotoxic effects of six different compounds (beta-carotene, lycopene, all-trans-, 9-cis- and 13-cis-retinoic acid and all-trans-retinol) on three breast cancer cell lines (MCF-7, MDA-MB-231, Hs578T cell lines).

As it is known, Scholar Google and similar databases are the most popular databases used for literature review. While reviewing the literature by using these databases, various keywords and keyword combinations related to the required study are used. Most of the time, tens of Scholar Google pages need to be scanned one by one, and each study in those pages needs to be looked at individually. When it is taken into account that there are hundreds of studies on breast cancer, this process is quite time-consuming for the researcher and may cause the studies needed by the researcher to escape the attention. Based on these disadvantages of Scholar Google and similar databases, we decided to design a relational database that brings together the literature centered on cytotoxically active compounds on breast cancer cells.

2.3. Creating Tables

To design the database, Microsoft Access (2007-2016 file format) was used. In the first step, five tables belonging to the database were created. These tables were named Publications, Cell Lines, Compounds, Treatments, and Cytotoxicity, respectively.

In the publications table, five columns were created, and these columns were named as publication ID, authors, publication year, publication name, and journal name, respectively. Publication ID was described as the primary key in this table. 80 publication records were entered into publications table. The first 21 rows of this table are shown in Figure 1.



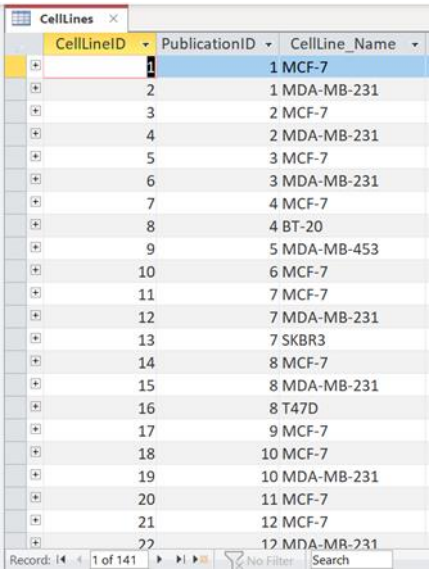
Publications

PublicationID	Authors	PublicationYear	PublicationName	JournalName
1	Alosi, J. A., McDoı	2010	Pterostilbene inhibits breast cancer in vitro through mi	Journal of Surgical Research
2	Atmaca, H., Bozku	2016	Effects of Galium aparine extract on the cell viability, ce	Journal of Ethnopharmacology
3	Bielawski, K., Czar	2013	Cytotoxicity and induction of apoptosis of human brea	Environmental Toxicology and Pharma
4	Chang, H. C., Chei	2011	Capsaicin may induce breast cancer cell death through	Human and Experimental Toxicology
5	Choi, E. J., & Kim,	2009	Apigenin induces apoptosis through a mitochondri	J.Clin.Biochem.Nutr.
6	Chou, C. C., Yang,	2010	Quercetin-mediated cell cycle arrest and apoptosis inv	Archives of Pharmacal Research
7	Choudhury, B., Ka	2018	Garcinia morella fruit, a promising source of antioxidar	Biomedicine & Pharmacotherapy
8	Damianaki, A., Ba	2000	Potent inhibitory action of red wine polyphenols on hu	Journal of Cellular Biochemistry
9	Duo, J., Ying, G. G	2012	Quercetin inhibits human breast cancer cell proliferatic	Molecular Medicine Reports
10	Elamin, M. H., Da	2013	Olive oil oleuropein has anti-breast cancer properties v	Food and Chemical Toxicology
11	Fan, P., Fan, S., W	2013	Genistein decreases the breast cancer stem-like cell po	Stem Cell Research & Therapy
12	Graidist, P., Martl	2015	Cytotoxic activity of Piper cubeba extract in breast canc	Nutrients
13	Gloria, N. F., Soar	2014	Lycopene and beta-carotene induce cell-cycle arrest an	Anticancer Research
14	Han, J., Talorete,	2009	Anti-proliferative and apoptotic effects of oleuropein a	Cytotechnology
15	Hu, H., Ahn, N. S.,	2002	Ganoderma lucidum extract induces cell cycle arrest ar	Int. J. Cancer
16	Hui, C., Bin, Y., Xia	2010	Anticancer activities of an anthocyanin-rich extract fro	Nutrition and Cancer
17	Jada, S. R., Matth	2008	Benzylidene derivatives of andrographolide inhibit gro	British Journal of Pharmacology
18	Khanavi, M., Nab	2010	Cytotoxic activity of some marine brown algae against	Biological Research
19	Khare, N., & Chan	2019	Stevioside mediated chemosensitization studies and cy	Saudi Journal of Biological Science
20	Chryssanthi, D. G	2007	Inhibition of breast cancer cell proliferation by style co	Anticancer Research
21	Lee, C. J., Wilson,	2010	Hesperidin suppressed proliferations of both human b	Phytotherapy Research
22	Li, Y., Zhang, T., K	2010	Sulforaphane, a dietary component of Broccoli/Brocco	Clinical Cancer Research

Record: 1 of 80 No Filter Search

Figure 1 Publications table

Into the cell lines table, breast cancer cell lines (such as MCF-7, MDA-MB-231, etc. are defined as “cell lines” in the related literature) used in the selected studies were entered. This table’s three columns were named as cell line ID, publication ID and cell line name. Cell line ID was described as the primary key in this table and unique for every individual breast cancer cell line used in every individual study. In this way, the confusion that may be caused by using the same breast cancer cell lines in more than one study was prevented. Totally, 141 records of breast cancer cell lines used in the selected studies were entered into this table. The first 21 rows of this table are shown in Figure 2.



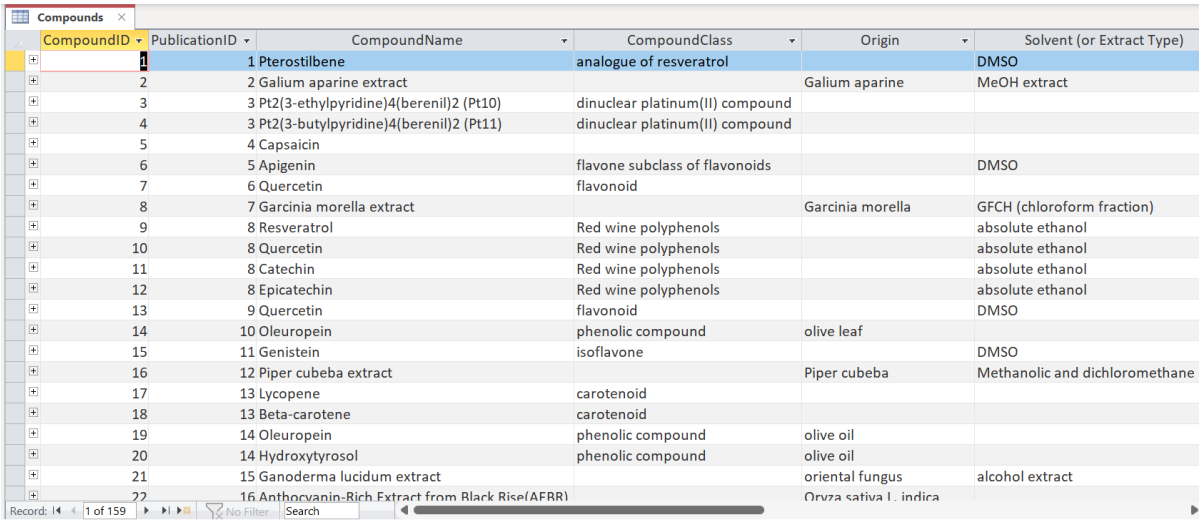
CellLines

CellLineID	PublicationID	CellLine_Name
1	1	MCF-7
2	1	MDA-MB-231
3	2	MCF-7
4	2	MDA-MB-231
5	3	MCF-7
6	3	MDA-MB-231
7	4	MCF-7
8	4	BT-20
9	5	MDA-MB-453
10	6	MCF-7
11	7	MCF-7
12	7	MDA-MB-231
13	7	SKBR3
14	8	MCF-7
15	8	MDA-MB-231
16	8	T47D
17	9	MCF-7
18	10	MCF-7
19	10	MDA-MB-231
20	11	MCF-7
21	12	MCF-7
22	12	MDA-MB-231

Record: 1 of 141 No Filter Search

Figure 2 Cell lines table

The compounds table was created to include the details of compounds used in the selected studies. Compound ID, publication ID, compound name, compound class, origin, solvent/extract type were the columns created in this table. If there was not any data about the class, origin, solvent, or extraction type of the compound in the relevant study, the part of the relevant column was intentionally left blank. Totally, 159 records of compounds were entered into this table. The first 21 rows of the compounds table are shown in Figure 3.



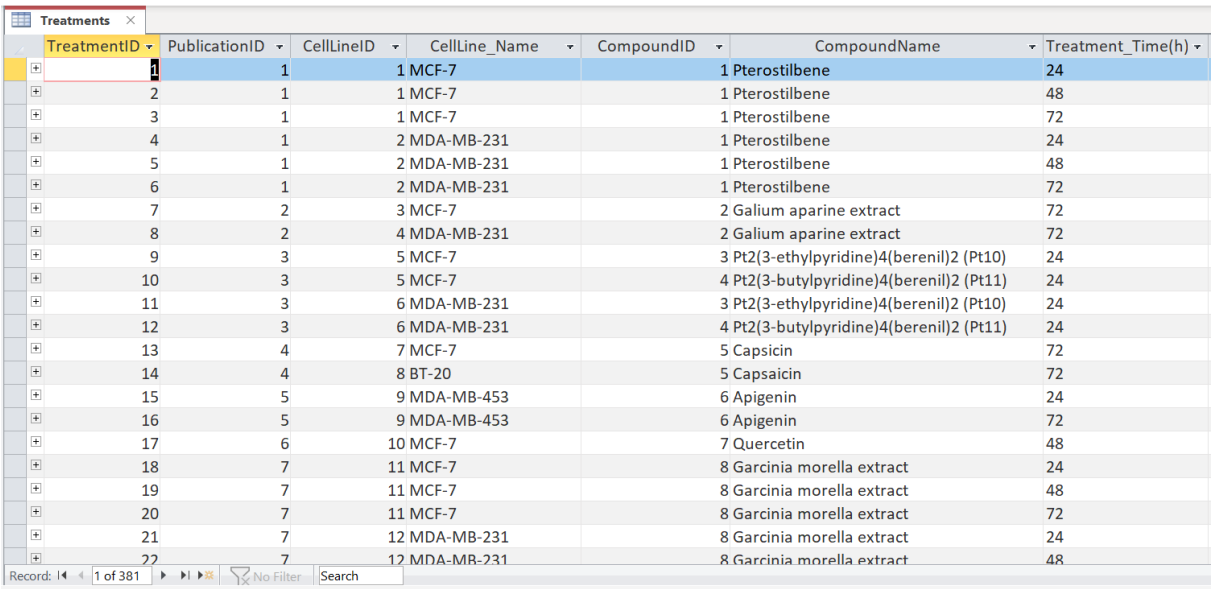
Compounds

CompoundID	PublicationID	CompoundName	CompoundClass	Origin	Solvent (or Extract Type)
1	1	Pterostilbene	analogue of resveratrol		DMSO
2	2	Galium aparine extract		Galium aparine	MeOH extract
3	3	Pt2(3-ethylpyridine)4(berenil)2 (Pt10)	dinuclear platinum(II) compound		
4	3	Pt2(3-butylpyridine)4(berenil)2 (Pt11)	dinuclear platinum(II) compound		
5	4	Capsaicin			
6	5	Apigenin	flavone subclass of flavonoids		DMSO
7	6	Quercetin	flavonoid		
8	7	Garcinia morella extract		Garcinia morella	GFCH (chloroform fraction)
9	8	Resveratrol	Red wine polyphenols		absolute ethanol
10	8	Quercetin	Red wine polyphenols		absolute ethanol
11	8	Catechin	Red wine polyphenols		absolute ethanol
12	8	Epicatechin	Red wine polyphenols		absolute ethanol
13	9	Quercetin	flavonoid		DMSO
14	10	Oleuropein	phenolic compound	olive leaf	
15	11	Genistein	isoflavone		DMSO
16	12	Piper cubeba extract		Piper cubeba	Methanolic and dichloromethane
17	13	Lycopene	carotenoid		
18	13	Beta-carotene	carotenoid		
19	14	Oleuropein	phenolic compound	olive oil	
20	14	Hydroxytyrosol	phenolic compound	olive oil	
21	15	Ganoderma lucidum extract		oriental fungus	alcohol extract
22	16	Anthocyanin-Rich Extract from Black Rice(ARBR)		Oryza sativa L. indica	

Record: 1 of 159 No Filter Search

Figure 3 Compounds table

The treatments table's primary key, treatment ID, is specific to breast cancer cell line-compound-treatment time combination. For instance, as seen in Figure 4, in the record of the publication which has Publication ID 1 [23], we see 6 different Treatment IDs belonging to it. The reason for this is that Pterostilbene is administered to MCF-7 and MDA-MB-231 breast cancer cell lines for three different administration periods and each administration period is represented by a unique Treatment ID (Treatment ID 1, 2, 3 for 24, 48, 72 h on MCF-7 and Treatment ID 4, 5, 6 for 24, 48, 72 h on MDA-MB-231 consecutively).



Treatments

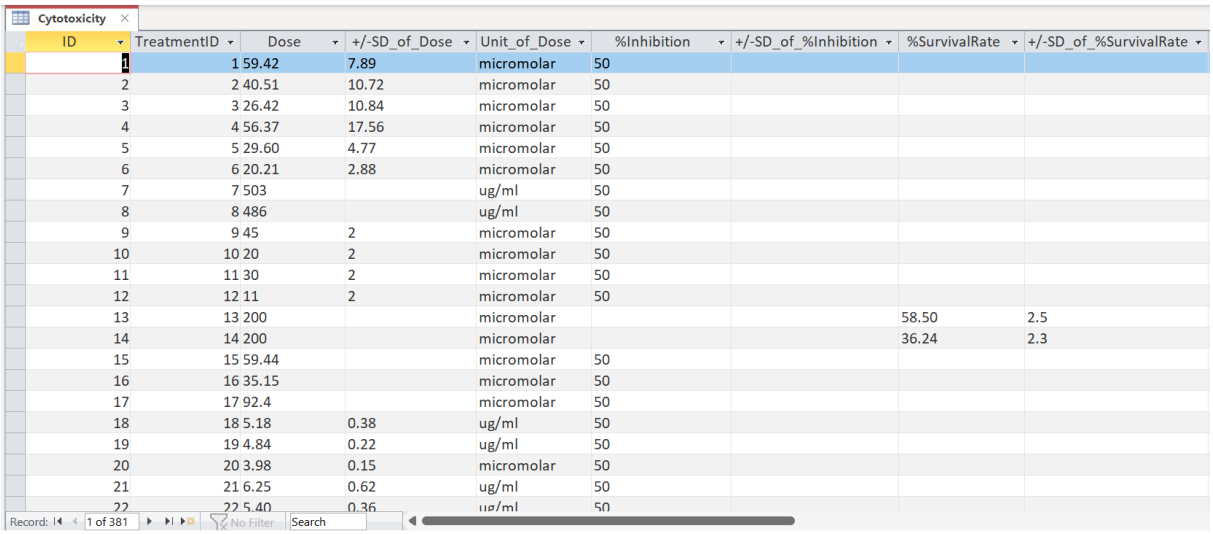
TreatmentID	PublicationID	CellLineID	CellLine_Name	CompoundID	CompoundName	Treatment_Time(h)
1	1	1	MCF-7	1	Pterostilbene	24
2	1	1	MCF-7	1	Pterostilbene	48
3	1	1	MCF-7	1	Pterostilbene	72
4	1	2	MDA-MB-231	1	Pterostilbene	24
5	1	2	MDA-MB-231	1	Pterostilbene	48
6	1	2	MDA-MB-231	1	Pterostilbene	72
7	2	3	MCF-7	2	Galium aparine extract	72
8	2	4	MDA-MB-231	2	Galium aparine extract	72
9	3	5	MCF-7	3	Pt2(3-ethylpyridine)4(berenil)2 (Pt10)	24
10	3	5	MCF-7	4	Pt2(3-butylpyridine)4(berenil)2 (Pt11)	24
11	3	6	MDA-MB-231	3	Pt2(3-ethylpyridine)4(berenil)2 (Pt10)	24
12	3	6	MDA-MB-231	4	Pt2(3-butylpyridine)4(berenil)2 (Pt11)	24
13	4	7	MCF-7	5	Capsicin	72
14	4	8	BT-20	5	Capsaicin	72
15	5	9	MDA-MB-453	6	Apigenin	24
16	5	9	MDA-MB-453	6	Apigenin	72
17	6	10	MCF-7	7	Quercetin	48
18	7	11	MCF-7	8	Garcinia morella extract	24
19	7	11	MCF-7	8	Garcinia morella extract	48
20	7	11	MCF-7	8	Garcinia morella extract	72
21	7	12	MDA-MB-231	8	Garcinia morella extract	24
22	7	12	MDA-MB-231	8	Garcinia morella extract	48

Record: 1 of 381 No Filter Search

Figure 4 Treatments table

The effects of compound administrations on breast cancer cell viabilities were entered into the cytotoxicity table as cytotoxicity data in the context of dose of compound, % inhibition, and % survival rate. In Figure 5, the cytotoxicity table and its columns are shown. With the purpose of creating columns

(fields) as simple and in atomic structure as possible, we placed unit of dose and standard deviations in separate columns. The cytotoxicity table has 381 records (rows) of cytotoxicity data.



Cytotoxicity

ID	TreatmentID	Dose	+/-SD_of_Dose	Unit_of_Dose	%Inhibition	+/-SD_of_%Inhibition	%SurvivalRate	+/-SD_of_%SurvivalRate
1	1	59.42	7.89	micromolar	50			
2	2	40.51	10.72	micromolar	50			
3	3	26.42	10.84	micromolar	50			
4	4	56.37	17.56	micromolar	50			
5	5	29.60	4.77	micromolar	50			
6	6	20.21	2.88	micromolar	50			
7	7	503		ug/ml	50			
8	8	486		ug/ml	50			
9	9	45	2	micromolar	50			
10	10	20	2	micromolar	50			
11	11	30	2	micromolar	50			
12	12	11	2	micromolar	50			
13	13	200		micromolar			58.50	2.5
14	14	200		micromolar			36.24	2.3
15	15	59.44		micromolar	50			
16	16	35.15		micromolar	50			
17	17	92.4		micromolar	50			
18	18	5.18	0.38	ug/ml	50			
19	19	4.84	0.22	ug/ml	50			
20	20	3.98	0.15	micromolar	50			
21	21	6.25	0.62	ug/ml	50			
22	22	5.40	0.36	ug/ml	50			

Record: 1 of 381 No Filter Search

Figure 5 Cytotoxicity table

The data extraction from the publications and the data input were carried out manually.

2.4. Creating Relationships Between Tables

The relationships between tables were created according to relationship defining instructions [24, 25]. The created relationships are shown in Figure 6.

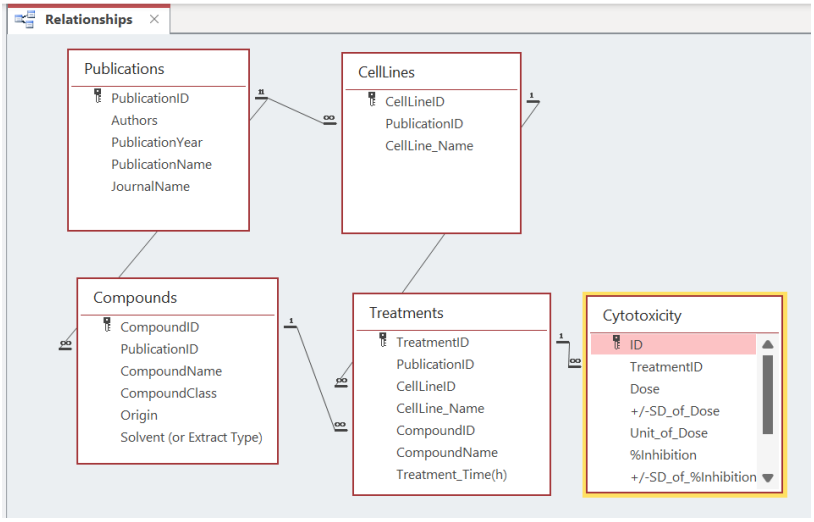


Figure 6 Relationships between tables

3. Results

When we queried with SQL, which breast cancer cell line was the most used one in 80 studies in our database, it was seen that MCF-7 was the most researched cell line with 64 studies. MDA-MB-231 cell line is following that with 34 studies. The SQL query for publications using MCF-7 cell line is shown in Figure 7 and first 25 of 64 results are seen in Figure 8.

MCF-7 and Publication Query

```
SELECT Publications.PublicationID, Publications.PublicationYear, Publications.PublicationName, CellLines.CellLine_Name
FROM Publications INNER JOIN CellLines ON Publications.[PublicationID] = CellLines.[PublicationID]
WHERE CellLine_Name='MCF-7';
```

Figure 7 SQL query for publications using MCF-7 cell line

MCF-7 and Publication Query

PublicationID	PublicationYear	PublicationName	CellLine_Name
1	2010	Pterostilbene inhibits breast cancer in vitro through mi	MCF-7
2	2016	Effects of Galium aparine extract on the cell viability, ce	MCF-7
3	2013	Cytotoxicity and induction of apoptosis of human brea	MCF-7
4	2011	Capsaicin may induce breast cancer cell death through	MCF-7
6	2010	Quercetin-mediated cell cycle arrest and apoptosis inv	MCF-7
7	2018	Garcinia morella fruit, a promising source of antioxidar	MCF-7
8	2000	Potent inhibitory action of red wine polyphenols on hu	MCF-7
9	2012	Quercetin inhibits human breast cancer cell proliferatic	MCF-7
10	2013	Olive oil oleuropein has anti-breast cancer properties v	MCF-7
11	2013	Genistein decreases the breast cancer stem-like cell po	MCF-7
12	2015	Cytotoxic activity of Piper cubeba extract in breast canc	MCF-7
13	2014	Lycopene and beta-carotene induce cell-cycle arrest an	MCF-7
14	2009	Anti-proliferative and apoptotic effects of oleuropein a	MCF-7
15	2002	Ganoderma lucidum extract induces cell cycle arrest ar	MCF-7
16	2010	Anticancer activities of an anthocyanin-rich extract fro	MCF-7
17	2008	Benzylidene derivatives of andrographolide inhibit gro	MCF-7
20	2007	Inhibition of breast cancer cell proliferation by style co	MCF-7
22	2010	Sulforaphane, a dietary component of Broccoli/Brocco	MCF-7
23	2017	Diosmin-induced senescence, apoptosis and autophag	MCF-7
24	2006	Antitumor activity of plant cannabinoids with emphasi	MCF-7
25	2004	In vitro anti-proliferative activities of ellagic acid	MCF-7
26	2015	Antitumor effects of crocin on human breast cancer ce	MCF-7

Record: 1 of 64 No Filter Search

Figure 8 Results of query for publications using MCF-7 cell line

Similar SQL queries were also performed for the compounds. Quercetin was found to be the most preferred compound among the studies in our database. The SQL query for publications using quercetin is shown in Figure 9 and the results are presented in Figure 10.

Quercetin and Publication Query

```
SELECT Publications.PublicationID, Publications.PublicationYear, Publications.PublicationName, Compounds.CompoundName
FROM Publications INNER JOIN Compounds ON Publications.[PublicationID] = Compounds.[PublicationID]
WHERE CompoundName='Quercetin';
```

Figure 9 SQL query for publications using quercetin

Quercetin and Publication Query

PublicationID	PublicationYear	PublicationName	CompoundName
6	2010	Quercetin-mediated cell cycle arrest and apoptosis inv	Quercetin
8	2000	Potent inhibitory action of red wine polyphenols on hu	Quercetin
9	2012	Quercetin inhibits human breast cancer cell proliferatic	Quercetin
40	2015	Apigenin inhibits growth of breast cancer cells: The rol	Quercetin
46	2015	Cytotoxic effect of Turkish propolis on liver, colon, bre	Quercetin

Figure 10 Results of query for publications using quercetin

4. Discussion

In the sense of user experience, this relational database has remarkable differences from the conventional literature search databases. Firstly, this database enables users to access compounds effective in breast cancer cells and the cytotoxic effect levels of these compounds together. For instance, a researcher who wants to review the cytotoxic effects of quercetin in breast cancer cells in conventional databases should perform a search with the keywords such as breast cancer, quercetin, cytotoxicity, and also look at every publication on the search pages one by one to see the cytotoxic analysis results.

On the other hand, a researcher using our relational database can access cytotoxic compounds, breast cancer cell lines in which these compounds are effective and cytotoxicity test results (in the context of numeric data) at the same time with SQL query commands quickly and easily. Continuing from the example of quercetin mentioned above, the researcher can see in which cell lines quercetin is administered, during which treatment time and in which dosage intervals it causes a cytotoxic effect.

In addition to these, with the help of this relational database, the most and the least investigated cell lines and compounds can be queried with simple SQL commands and the popular study focuses can be specified.

5. Conclusion and Future Works

Cytotoxic analyses are critical in drug development. Especially in the investigation of new cancer therapeutics, it is essential to identify compounds with cytotoxic effects on cancer cells. Studies analyzing the cytotoxic effects of the compounds with anti-cancer properties on different cancer cells constitute a very rich source of data. However, there is no database where researchers can collectively access the results of these studies in the context of cell type-compound-dose and % inhibition. This database we have designed for the compounds possessing cytotoxic effects on breast cancer cells is the first one in this sense.

The data in this database has the potential to be updated and enriched continuously by the inclusion of new publications in the literature. It is planned to make the database accessible to the end-user in the internet environment. In this way, this database will be a reference source for researchers, who want to design a study on breast cancer, where they can see cytotoxic compounds and the studies made with these compounds collectively, and also save time in the literature search step.

With the experience gained in designing a relational database while creating this database prototype, similar databases can be designed for the investigations on other cancer types in the future.

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