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Drug Discovery
2024



Pitirim Sorokin
SYKTYVKAR STATE UNIVERSITY

CHRONOBIOTICSDB -

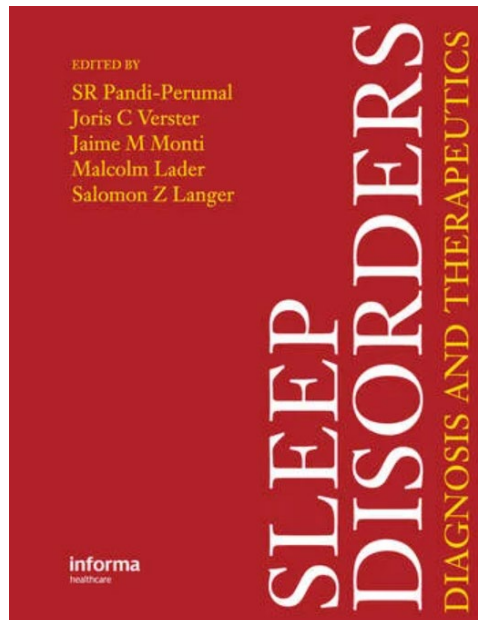
WORLD FIRST DATABASE OF CIRCADIAN RHYTHM'S PHARMACOLOGICAL
MODULATORS

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DEFINITION

- Chronobiotic refers to a substance that has the ability to alter the phase of the circadian time system, thereby re-establishing and synchronizing circadian rhythms that have been disrupted in the short or long term.
- From: Sleep Disorders [2019], Rethinking the use of hypnotics for treatment of insomnia in the elderly [2021]



EXPERT OPINION ON PHARMACOTHERAPY
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EDITORIAL

Rethinking the use of hypnotics for treatment of insomnia in the elderly

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KEYWORDS Elderly; hypnotic; insomnia; sleep

1. Introduction

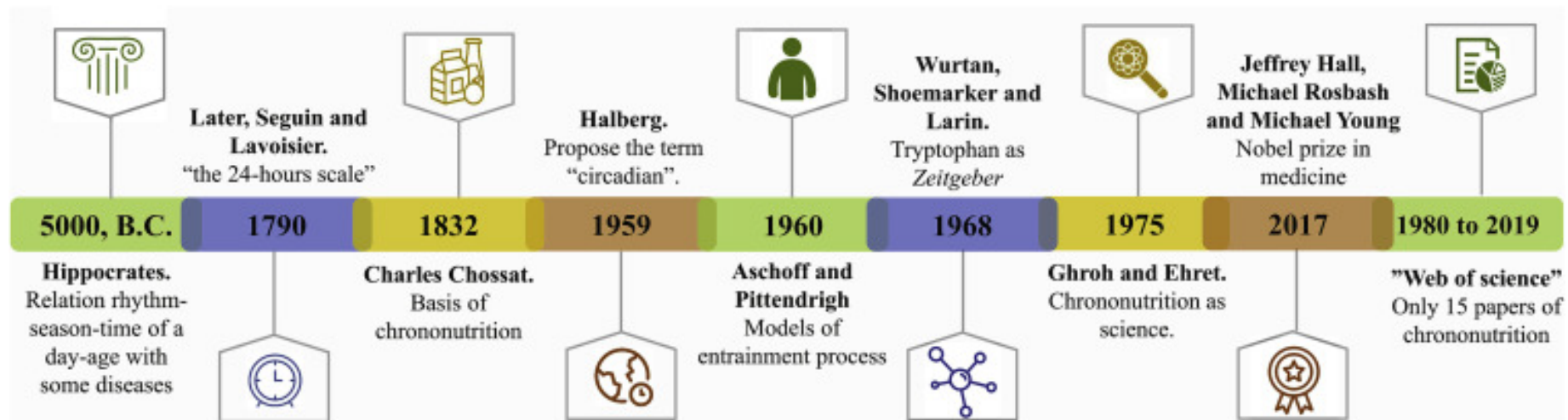
In all living creatures, a predetermined period of endogenously driven motor inactivity occurs during the 24-h day [1,2]. Mostly, this period coincides with the time creatures could be in danger; for example, species that use their eyes to detect enemies are in danger during the dark night. Another evolutionary fact is that during this time of inactivity, creatures respond only to individually relevant, learned events. In humans, for instance, a mother is more likely to awaken at the slightest whisper from her new-born child than to a loud noise, whereas the father sleeping next to her may react in the

sleep period differs in length from individual to individual, sleep stages in healthy subjects occur in a stereotypic pattern. The complexity in particular of the neural mechanisms behind these coordinated processes cannot be overestimated [3,4]. Changes in any of these processes during sleep result in specific disturbances and functional deficits that can lead to impaired well-being, performance and health [5,7–9].

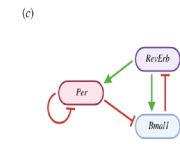
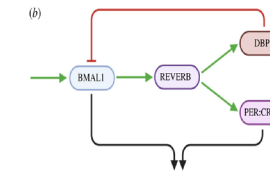
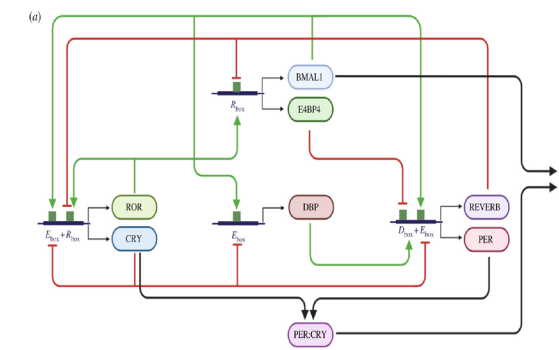
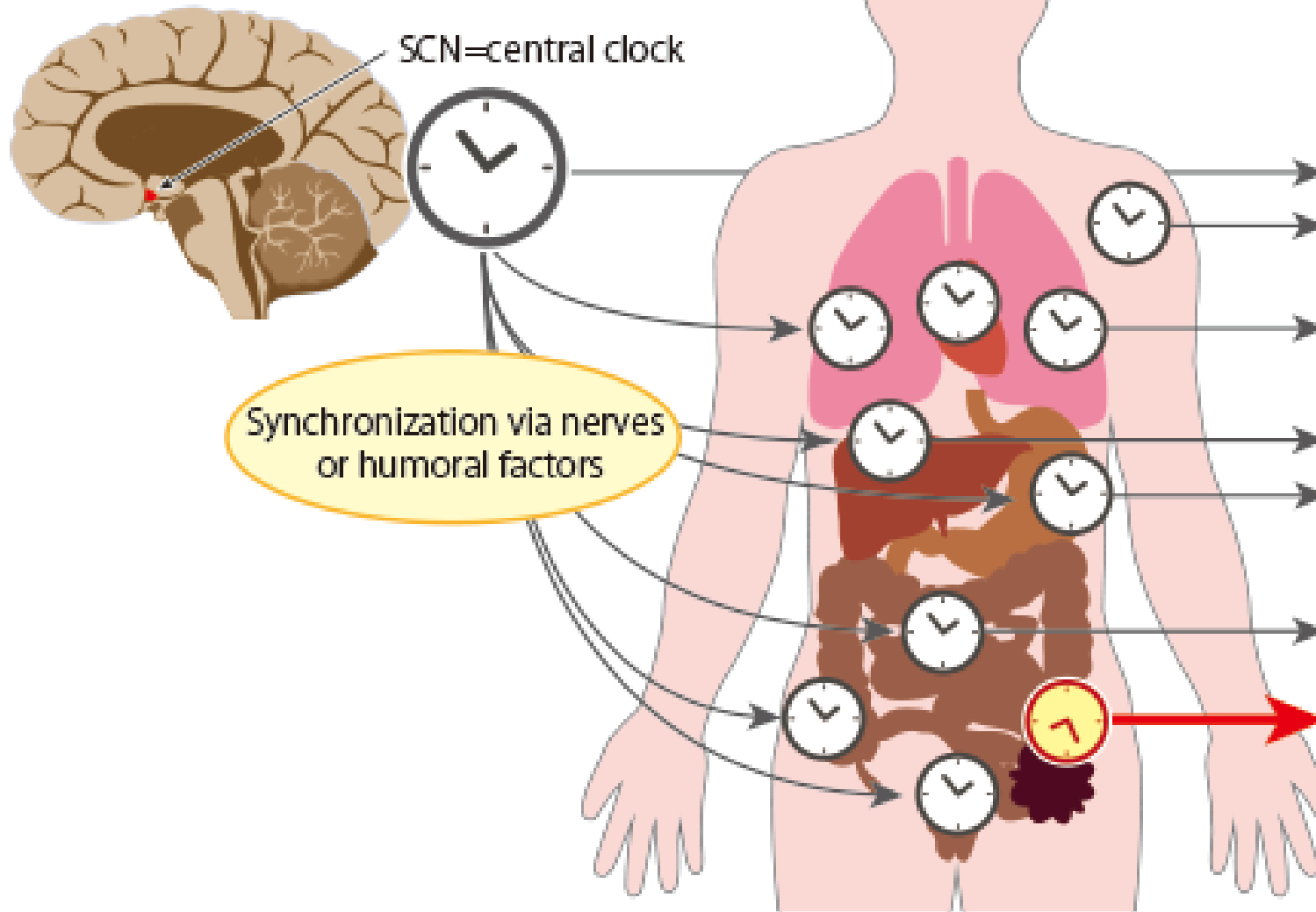
A common belief is that humans need less sleep as they age. No evidence for this exists, however. Indeed, it is more likely that age-related disorders (co)affecting the nervous system, as well as psychotropic medications, spoil the quality of sleep, leading to an increased need for sleep time in order to

HISTORY AND ACTIVITY

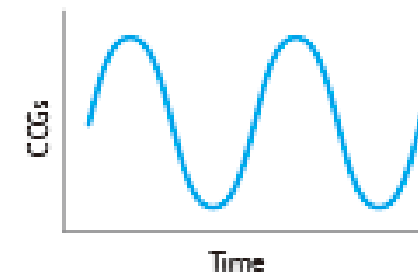
- Chronobiotics are drugs, both experimental and used in medical practice, constituting a rather heterogeneous group of substances that can modify the parameters of the circadian rhythm of fluctuations in various physiological and biochemical parameters, such as the expression of the “clock” genes themselves in organisms-models and cell cultures or the expression of clock-controlled genes.
- The class of chronobiotic drugs has been known for more than 50 years, since the properties of the hormone melatonin were discovered and described in detail in the clinic. Chrononutrition was also defined as science only in 1975.



PHYSIOLOGICAL CLOCK

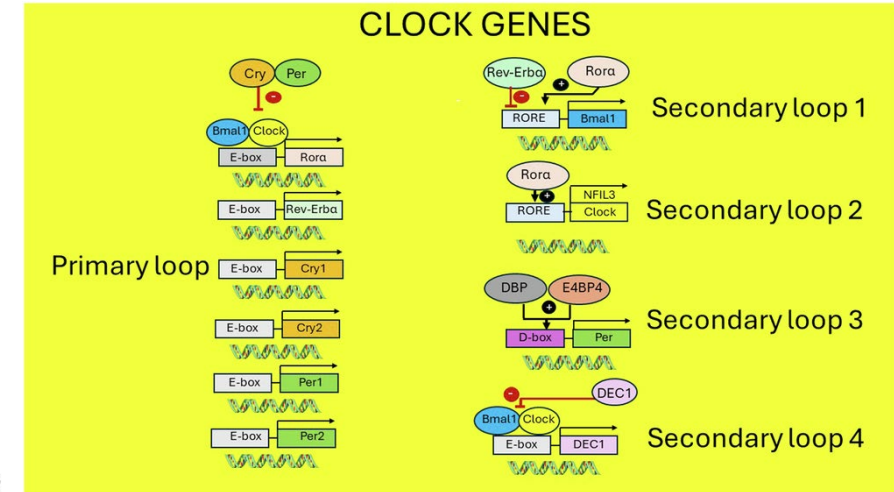
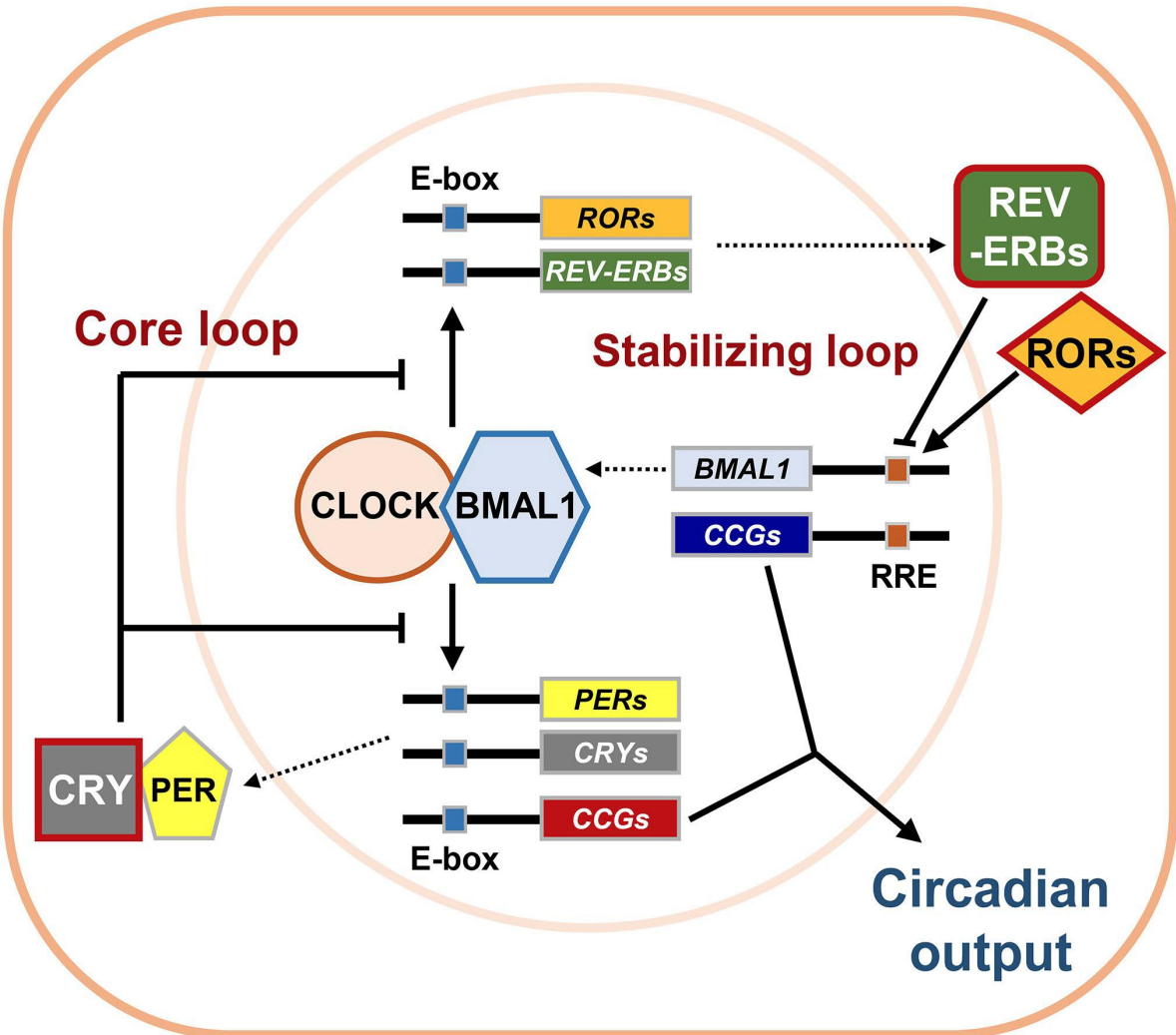


Clock output = CCG expression



- Diseases related to the disruption of circadian rhythm
- Cancer
 - Depression
 - Sterility
 - Sleep disturbance
 - Metabolic syndromes

CIRCADIAN CORE CLOCK AND ITS PHARMACOLOGY



CRYs

- Natural ligand: None
- Stabilizer/activator: KL001 & derivatives
- Inhibitor: KS15

REV-ERBs

- Natural ligand: Heme
- Agonist: GSK4112, SR9009/9011, GSK2945
- Antagonist: SR8278

RORs

- Natural ligand: Oxysterols (α/γ), Retinoic acids (β)
- Agonist: SR1078, Nobiletin
- Inverse agonist: T0901317, SR1001

PROBLEMS



- Despite attempts to systematize chronobiotics, there is not yet a unified classification of these pharmacological agents (natural chrononutrients, synthetic targeted circadian rhythm modulators, hypnotics, chronobiotic hormones are identified)
- There is no main source of knowledge on chronobiotics



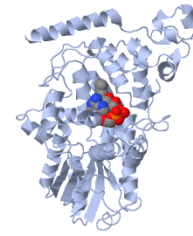
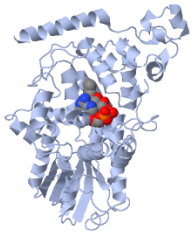
SOLUTION

- Creation of the world first curated and updated database of chronobiotic compounds (circadian rhythm modulators) and organization of access to it is an urgent fundamental task of chronobiology, chronomedicine and pharmacoinformatics (bioinformatics).

AIM

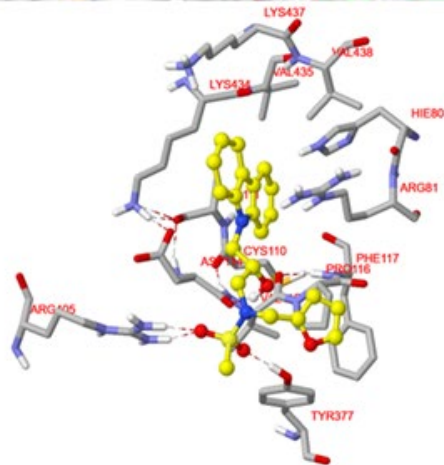
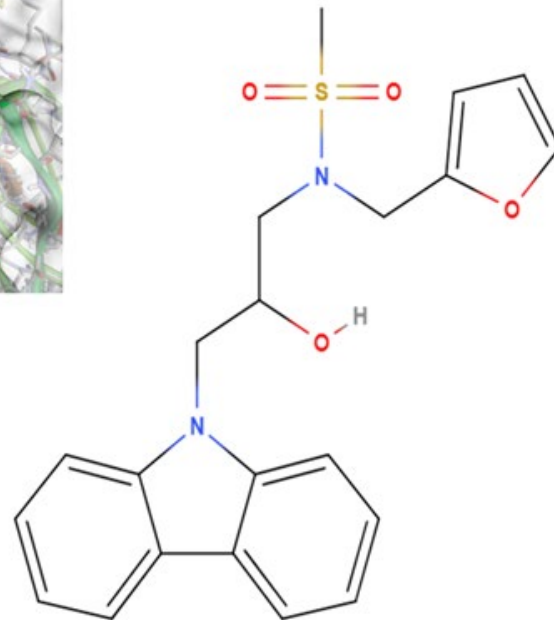
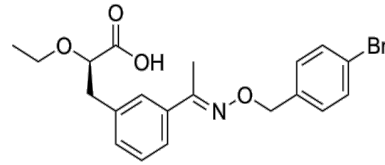
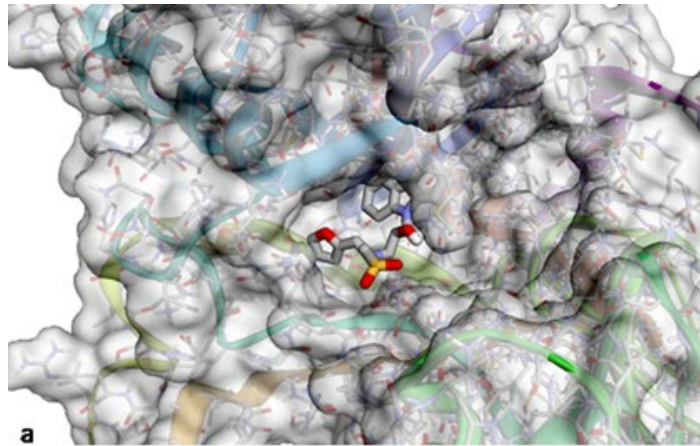
- The purpose of the study is to create a relational database of chronobiotics "ChronobioticsDB" (future domain cb-db.ru)

SOURCE OF INSPIRATION FOR DATABASE: CRYPTOCHROMES AND THEIR INHIBITORS



Jmol

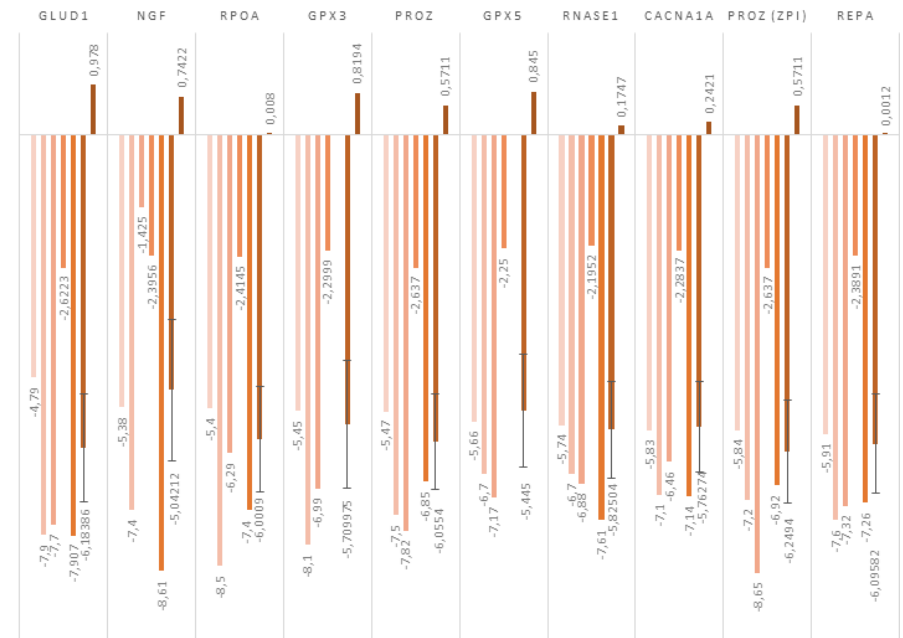
Jmol



b

c

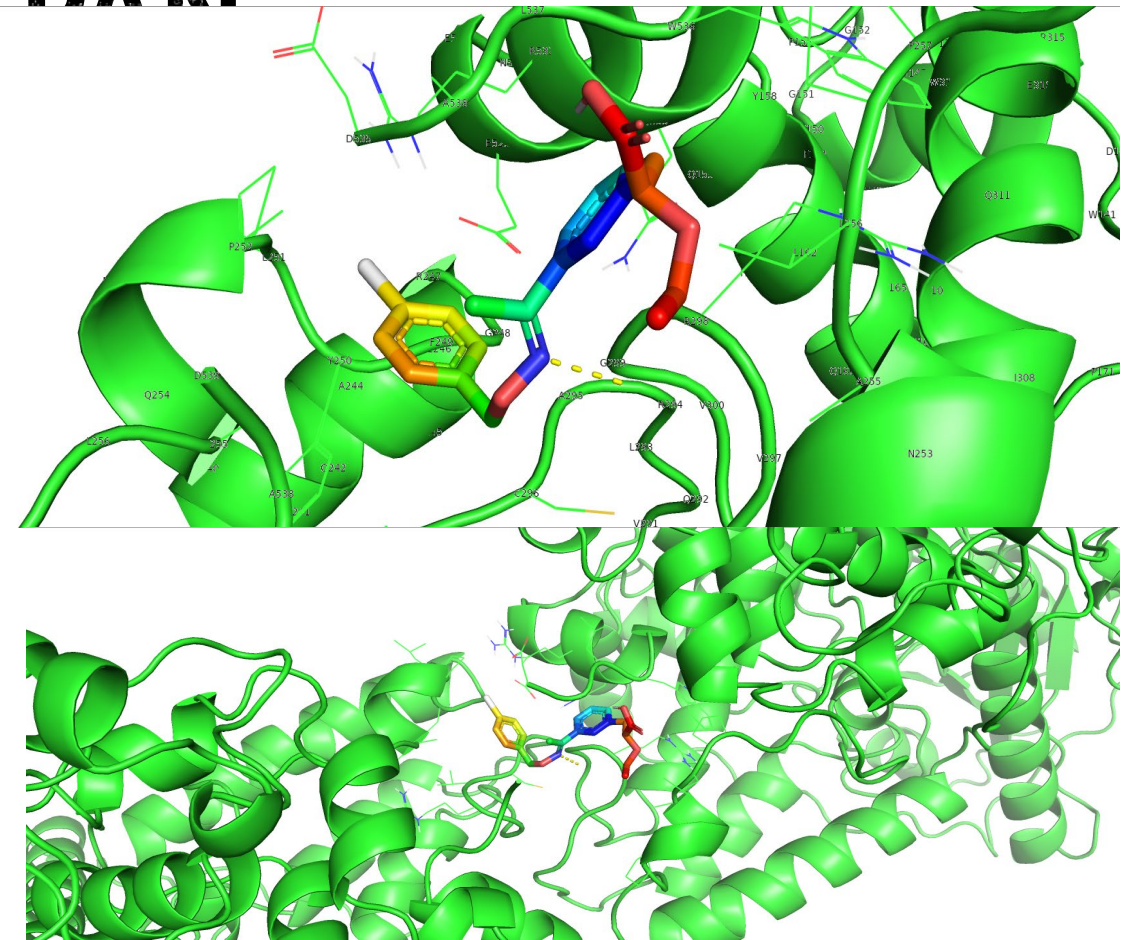
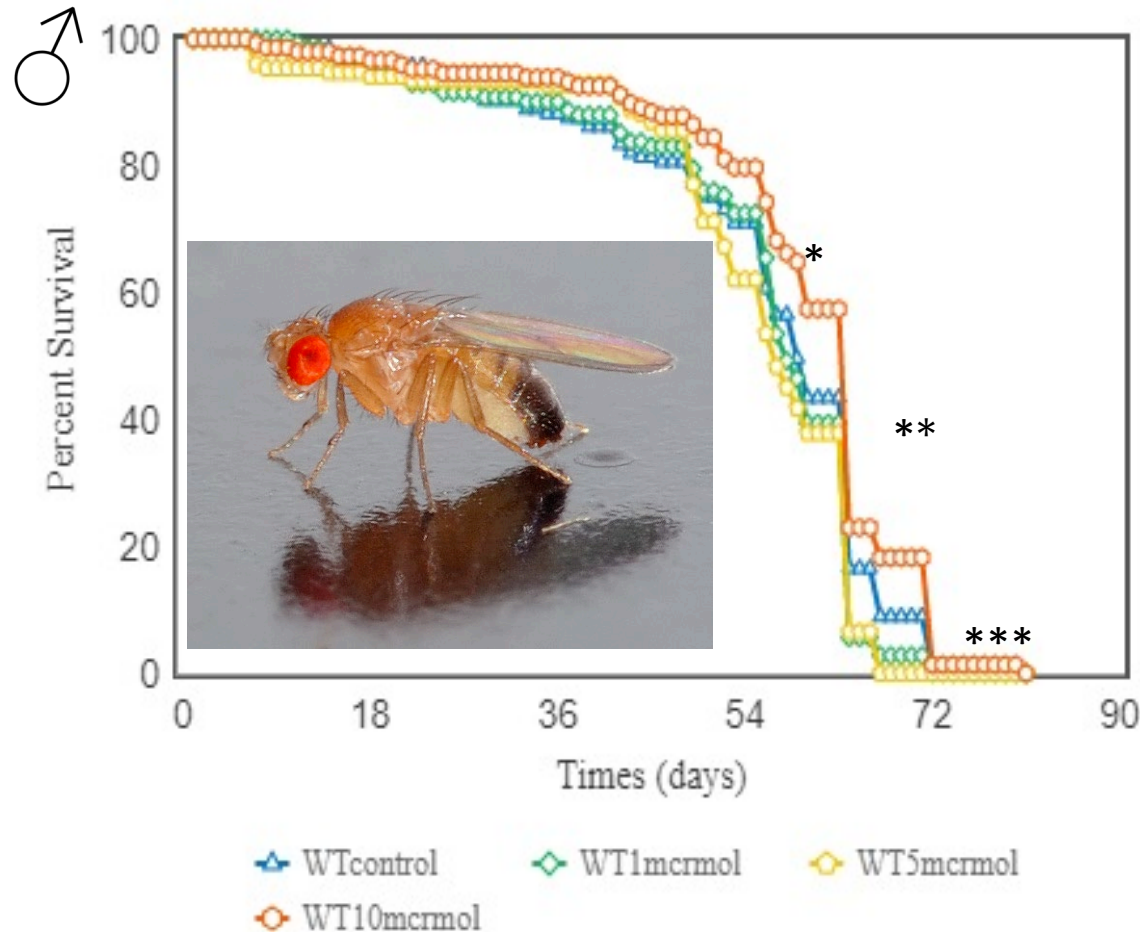
■ ACID, kcal/mol ■ Vina, kcal/mol ■ AutoDock4, kcal/mol
■ JAMDA, kcal/mol ■ Swissdock, kcal/mol ■ Mean ΔG, kcal/mol
■ Bindscope probability score, fraction



d

CRYPTOCHROME INHIBITOR KS15 (0,1% DMSO) EXTENDS DROSOPHILA

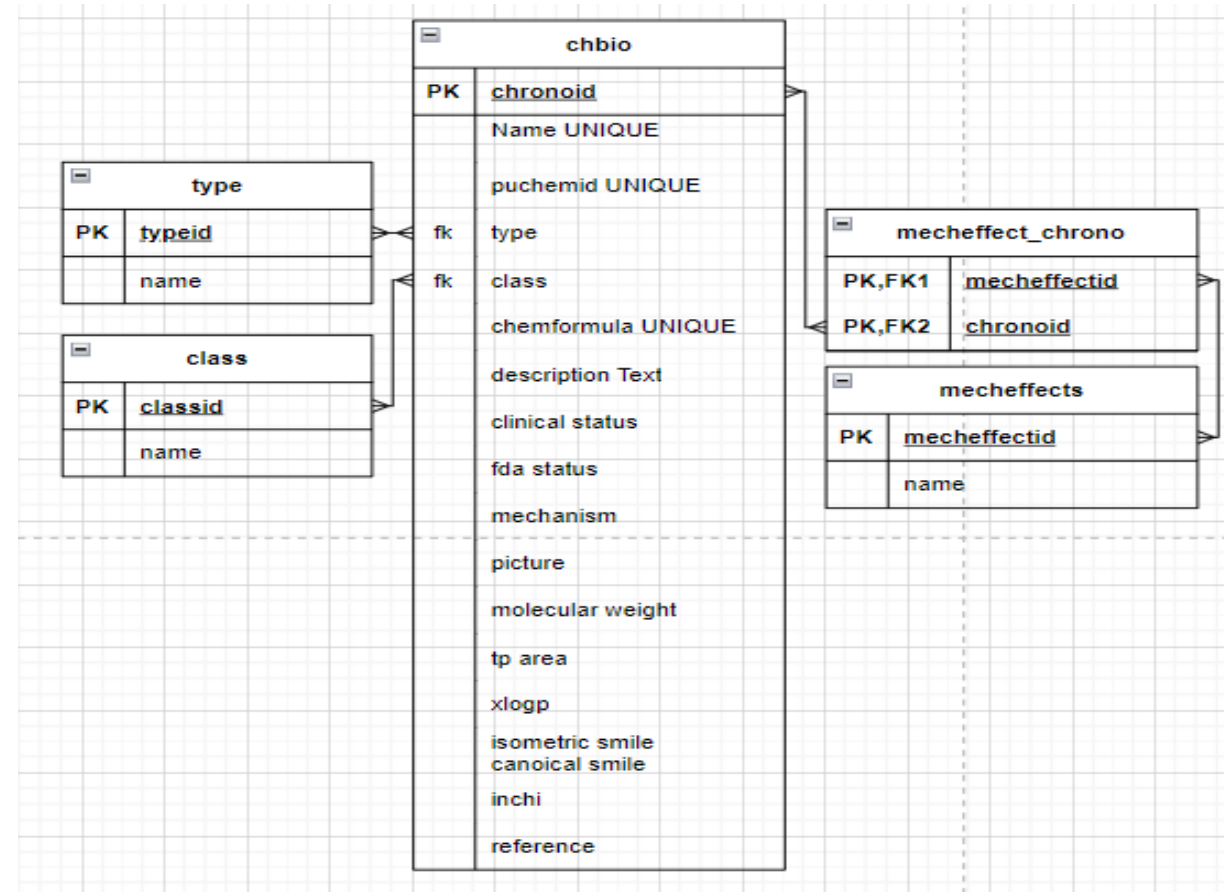
I I E E S D A N



*- $p < 0.01$, according to χ^2 ; **- $p < 0.01$ (Gehan-Breslow-Wilcoxon); ***- $p < 0.05$ Wang Allison test.
 Solovev, I.A., Shaposhnikov, M.V., Moskalev, A.A. (2021) *Clocks & Sleep*, 3, 429-441.

MATERIALS AND METHODS

- php programming language as a key tool, JAVA as facultative
- MySQL, PostgreSQL as a database management system
- The ChronobioticsDB is filled using PubMed data on chronobiotics which are manually extracted from articles and annotated
- The cards of chronobiotics are filled semiautomatically using key sources



DATABASE MANAGEMENT SYSTEM

The screenshot displays the pgAdmin 4 interface. The top menu bar includes 'File', 'Object', 'Tools', and 'Help'. The 'Object Explorer' on the left shows a tree view of database objects, with 'Tables (9)' expanded to show a 'chbio' table. A context menu is open over the 'chbio' table, with 'View/Edit Data' selected, which has opened a sub-menu showing options like 'All Rows', 'First 100 Rows', and 'Last 100 Rows'. The main window shows a query editor with the following SQL query:

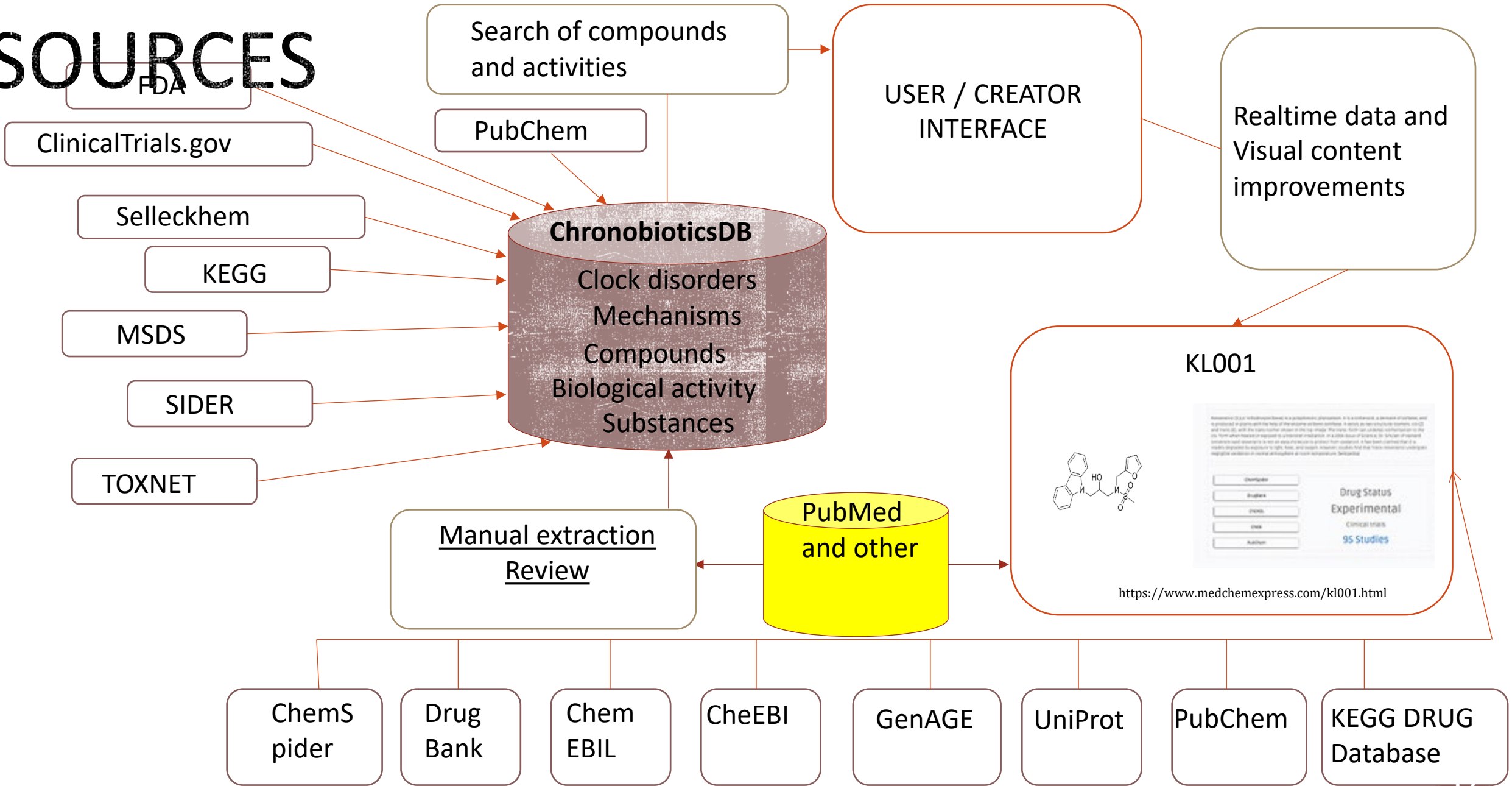
```
1 SELECT * FROM public.chbio
2 ORDER BY chronoid ASC
```

Below the query editor, the 'Data Output' section shows a table with the following columns and data types:

chronoid	name	puchemid	chemformula	description	mechanism	picture
[PK] integer	character varying (64)	integer	character varying	character varying	character varying	byte

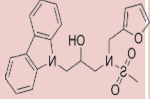
The status bar at the bottom indicates 'Total rows: 0 of 0', 'Query complete 00:00:00.182', and 'Ln 1, Cc'.

DATA SOURCES



DATA MODEL

CBDB ID	Name	SMILES	PUBCHEM link	Synonyms
0001	KL001	<chem>CS(=O)(=O)N(CC1=CC=CO1)CC(CN2C3=CC=CC=C3C4=CC=CC=C42)O</chem>	https://pubchem.ncbi.nlm.nih.gov/compound/kl001	N-(3-(9H-carbazol-9-yl)-2-hydroxypropyl)-N-(furan-2-ylmethyl)methanesulfonamide
0002	KS15

CBDB ID	MW	Molecular Formula	IMAG E
0001	398.48	C ₂₁ H ₂₂ N ₂ O ₄ S	
0002			

CBDB ID	Effect 1	Effect 2	Effect N
0001	<u>Period length alteration</u>	Lifespan extension	Perion restoration

CBDB ID	Paper 1	Paper 2	Paper N
0001	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589997/	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589997/	
0002			

ID CBDB	Target	PDB ID	Alt. target	Toxicity	Class
0001	CRY1	7D19	NG F1		mode rate	3

TABLE REPRESENTATION

Warning: foreach() argument must be of type array/object, bool given in C:\xampp\htdocs\chrono\data.php on line 42

#	Name	Image	Class	Formula	Smiles	Description	Clinical trials	FDA status	Article	Pubchem	Chemspider	Drugbank	Chebi	Chembil	Uniprot	Engage	Kegg	MSDS	Sider	Toxnet	Sellec
---	------	-------	-------	---------	--------	-------------	-----------------	------------	---------	---------	------------	----------	-------	---------	---------	--------	------	------	-------	--------	--------

[Upload new chronobiotic](#)

The screenshot shows a database management interface with a table structure view for the 'chronobiotics' table. The table has 18 columns, each with a unique identifier, name, type, comparison, null attributes, and actions for change and delete. The columns are: idchrono (int(5), auto-increment), name (varchar(32)), moleculaimg (blob), molecula (varchar(64)), smiles (varchar(64)), description (varchar(512)), fdastatus (varchar(32)), article (varchar(64)), pubchem (varchar(64)), chemspider (varchar(64)), drugbank (varchar(64)), chebi (varchar(64)), chembil (varchar(64)), uniprot (varchar(64)), engage (varchar(64)), kegg (varchar(64)), msds (varchar(64)), and sider (varchar(64)).

#	Name	Type	Comparison	Null Attributes	By Default	By default	Comments	Additionally	Action
<input type="checkbox"/>	1 idchrono	int(5)		No	no	η		Auto_increment	Change Delete More
<input type="checkbox"/>	2 name	varchar(32)	utf8mb4_general_ci	No	no	η			To change Delete More
<input type="checkbox"/>	3 moleculaimg	blob		Yes	NULL				To change Delete More
<input type="checkbox"/>	4 molecula	varchar(64)	utf8mb4_general_ci	No	no	η			To change Delete More
<input type="checkbox"/>	5 smiles	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	6 description	varchar(512)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	7 fdastatus	varchar(32)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	8 article	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	9 pubchem	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	10 chemspider	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	11 drugbank	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	12 chebi	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	13 chembil	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	14 uniprot	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	15 engage	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	16 kegg	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	17 msds	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More
<input type="checkbox"/>	18 sider	varchar(64)	utf8mb4_general_ci	Yes	NULL				To change Delete More

Console:
 >SELECT FROM "chronobiotics"
 >ALTER TABLE classes ADD CONSTRAINT chrid FOREIGN KEY (chrid) REFERENCES chronobiotics(idchrono);

«SUBMIT CHRONOBIOTIC» DIRECTORY

localhost/chrono/

Name :

image :

Class :

Formula :

SMILES :

Description :

Clinical status :

Fda status :

Artucle :

Pubchem :

Chemspider :

Drugbank :

Chebi :

Chembil :

Uniprot :

Engage :

Kegg :

MSDS :

Sider :

Toxnet :

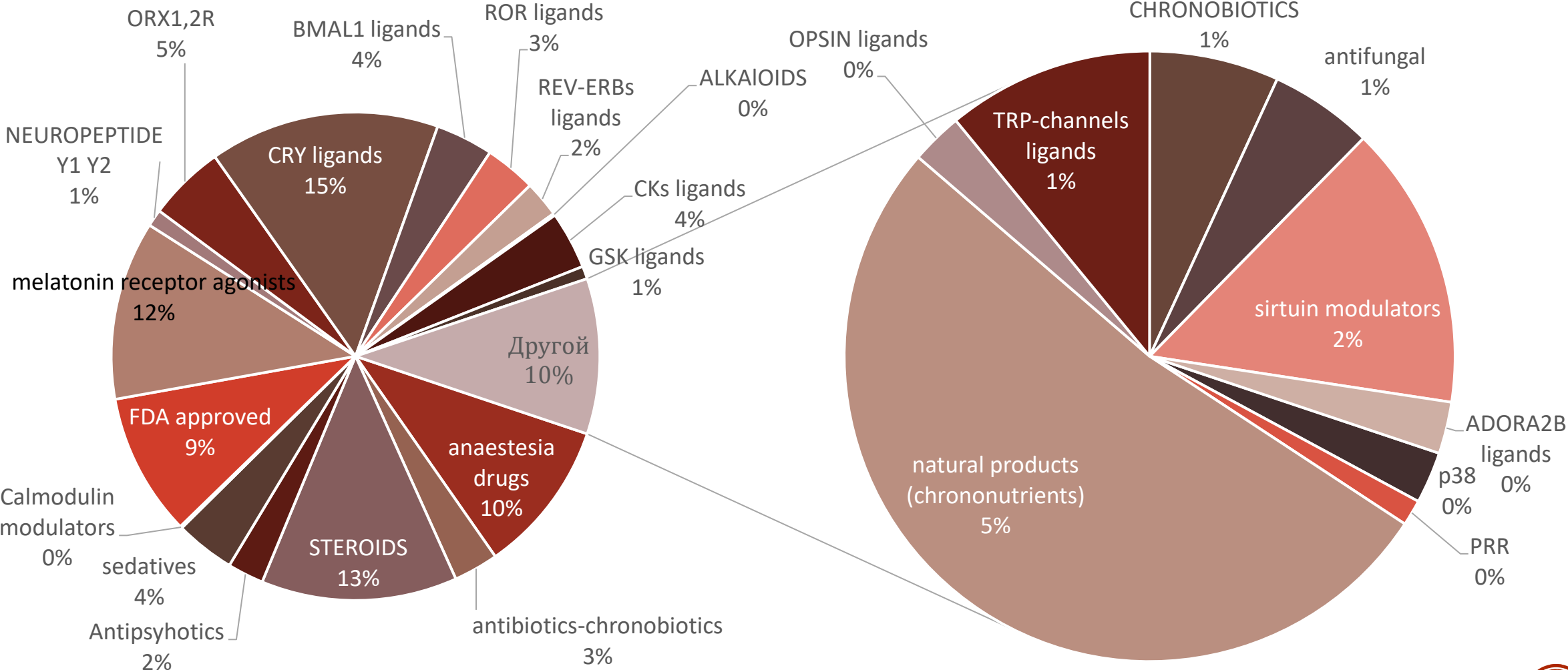
Selleckchem :

[Data](#)

```
data.php
5 <html lang="en" dir="ltr">
10 <body>
11 <table border = 1 cellspacing = 0 cellpadding = 10>
12 <tr>
13 <td></td>
16 <td>Class</td>
17 <td>Formula</td>
18 <td>Smiles</td>
19 <td>Description</td>
20 <td>Clinical trials</td>
21 <td>FDA status</td>
22 <td>Article</td>
23 <td>Pubchem</td>
24 <td>Chemspider</td>
25 <td>Drugbank</td>
26 <td>Chebi</td>
27 <td>Chembil</td>
28 <td>Uniprot</td>
29 <td>Engage</td>
30 <td>Kegg</td>
31 <td>MSDS</td>
32 <td>Sider</td>
33 <td>Toxnet</td>
34 <td>Selleckchem</td>
35 </td>
36 </tr>
37 </body>
38 </html>
39 <?php
40 $i = 1;
41 $rows = mysqli_query($conn, "SELECT * FROM chronodb ORDER BY idchrono DESC")
42 <?php foreach ($rows as $row) : ?>
43 <tr>
44 <td><?php echo $i++; ?></td>
45 <td><?php echo $row["name"]; ?></td>
46 <td><?php echo $row["moleculaimg"]; ?> width = 200 title="<?php echo $row['moleculaimg']; ?>" /></td>
47 <td><?php echo $row["molecula"]; ?></td>
48 <td><?php echo $row["smiles"]; ?></td>
```

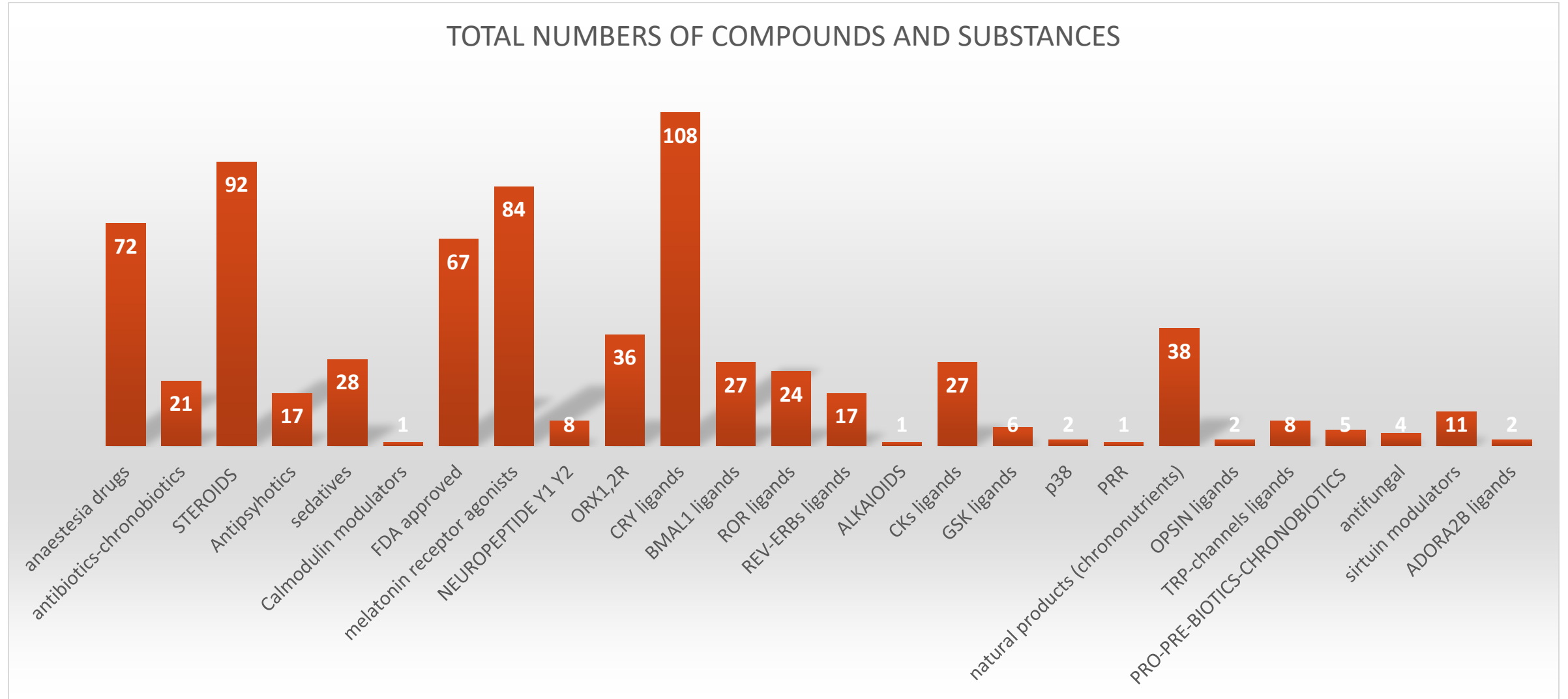
CONTENT

Distribution of drugs among classes



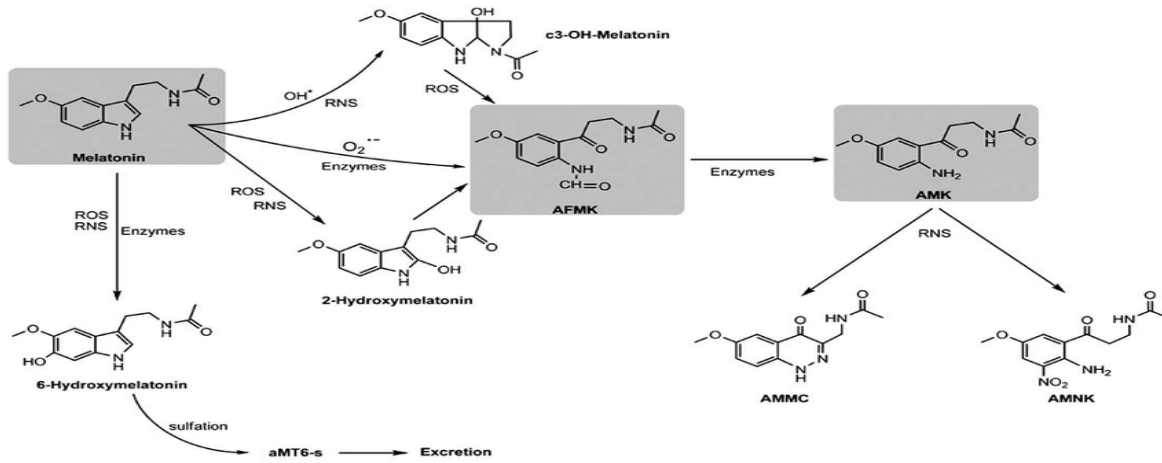
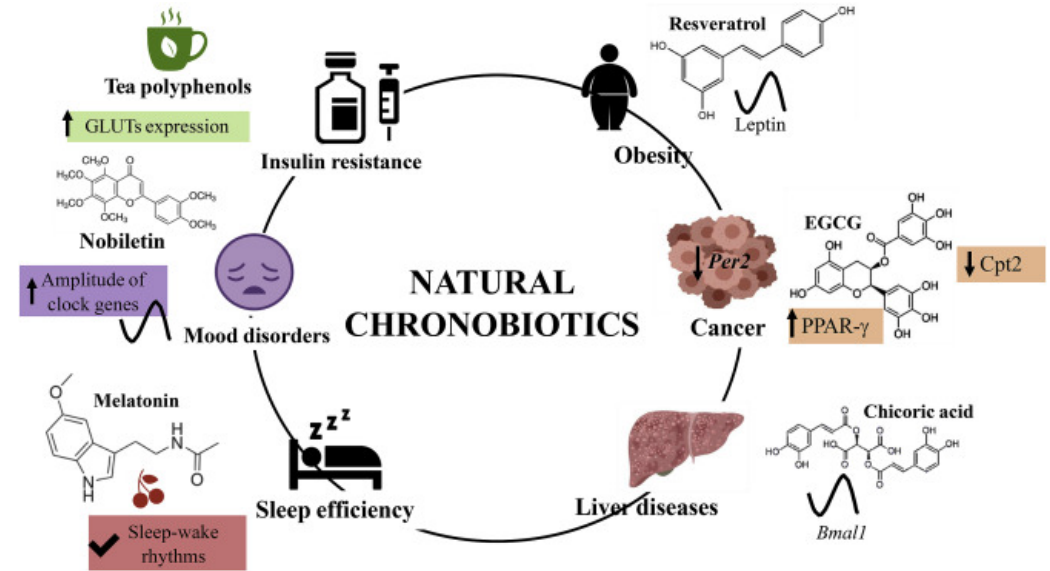
CONTENT

TOTAL NUMBERS OF COMPOUNDS AND SUBSTANCES



CLASSIFICATIONS OF COMPOUNDS IN CHRONOBIOLOGICSDB

- Target-oriented (leading)
- Activity-oriented
- Clinically-approved status
- Chronotoxicity-oriented
- Structure based (in development)



CONCLUSION

- The ChronobioticsDB will start functioning on CB-DB.ru all over the world at the end of 2024
- ChronobioticsDB is growing every day and already having more than 450 compounds with
- The database will have «SUBMIT» directory for any researcher to apply with new compound with chronobiotic traits which are proved in experiments (*in vivo* or *in silico*)
- ChronobioticsDB will become a key instrument to create a training set for machine learning tool searching for novel chronobiotics of different classes in Synthetically Accessible Virtual Inventory (SAVI)

ACKNOWLEDGEMENTS



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Foundation**

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TRANSLATIONAL BIOINFORMATICS AND SYSTEMS BIOLOGY LAB



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- Dr. Nadezhda O. Kotelina (PhD in Mathematics, Assistant professor of the Applied mathematics department)



- Denis A. Golubev (PhD student Life Sciences, Biogerontology)



- Arina I. Yagovkina (Student, Applied mathematics)

THANK YOU FOR ATTENTION

LITERATURE

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