

E-ISSN: 1306-4001

www.marmaraonline.com

Volume 21 • Issue 1 • January 2017

# Marmara Pharmaceutical Journal

AN INTERNATIONAL OPEN ACCESS JOURNAL OF  
PHARMACY AND PHARMACEUTICAL SCIENCES

Vol. 21 (1)  
2017

**Editorial Board**

Prof. Christoph

Prof. Tuncel

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz

Prof. Yilmaz



MARMARA  
UNIVERSITY

Marmara  
Pharm J

# Journal of Research in Pharmacy

An international open-access journal of pharmacy and pharmaceutical sciences  
Formerly published as Marmara Pharmaceutical Journal

(<https://jrespharm.com/>)

# JRP

ISSN : 1309-0801



[Current Issue \(https://jrespharm.com/content.php?id=82\)](https://jrespharm.com/content.php?id=82)

[Articles in Press \(https://jrespharm.com/content.php?id=46\)](https://jrespharm.com/content.php?id=46)

[Archive \(https://jrespharm.com/archive.php\)](https://jrespharm.com/archive.php)

[Search \(https://jrespharm.com/search.php\)](https://jrespharm.com/search.php)

[Author Benefits \(https://jrespharm.com/static.php?id=11\)](https://jrespharm.com/static.php?id=11)

## Editor-in-Chief

Hatice Kübra Elçioğlu

## Vice Editors

Levent Kabasakal

Esra Tatar

## Online ISSN

2630-6344

## Publisher

Marmara University

## Frequency

Bimonthly (Six issues / year)

## Abbreviation

J.Res.Pharm.

## Former Name

Marmara Pharmaceutical Journal

## Editorial Board

### *Editor-in-Chief*

#### **Hatice Kübra ELÇİOĞLU**

Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
kubra.elcioglu@marmara.edu.tr (mailto:kubra.elcioglu@marmara.edu.tr)

### *Vice Editors*

#### **Levent KABASAKAL**

Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
lkabasakal@marmara.edu.tr (mailto:lkabasakal@marmara.edu.tr)

#### **Esra TATAR**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
etatar@marmara.edu.tr (mailto:etatar@marmara.edu.tr)

### *Analytical Chemistry & Therapeutic Drug Monitoring*

#### **Anil Kumar DWIVEDI**

Central Drug Research Institute, Lucknow, India  
anilcdri@gmail.com (mailto:anilcdri@gmail.com)

#### **Anisa ELHAMILI**

Department of Medicinal & Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya  
aaelhamili2000@gmail.com (mailto:aaelhamili2000@gmail.com)

#### **Emirhan NEMUTLU**

Department of Analytical Chemistry, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye  
enemutlu@hacettepe.edu.tr (mailto:enemutlu@hacettepe.edu.tr)

#### **Lorena MEMUSHAJ**

Department of Pharmacy, Faculty of Medical Sciences, Aldent University, Tirana, Albania  
lorena.memushaj@ual.edu.al (mailto:lorena.memushaj@ual.edu.al)

#### **Mehmet GÜMÜŞTAŞ**

Department of Forensic Toxicology, Institute of Forensic Sciences, Ankara University, Ankara, Türkiye  
mgumustas@hotmail.com (mailto:mgumustas@hotmail.com)

#### **Mohd Younis RATHER**

Multidisciplinary Research Unit, Government Medical College Srinagar, Srinagar, India  
younis.rather78@gmail.com (mailto:younis.rather78@gmail.com)

### **Pablo MIRALLES IBARRA**

1. Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO-Public Health), Valencia, Spain

2. Department of Analytical Chemistry, Faculty of Chemistry, University of Valencia, Burjassot, Spain miralles\_pabiba@gva.es (mailto:miralles\_pabiba@gva.es)

### **Pınar TALAY PINAR**

Department of Analytical Chemistry, Faculty of Pharmacy, Yüzüncü Yıl University, Van, Türkiye ptalay@gmail.com (mailto:ptalay@gmail.com)

### *Biochemistry & Cancer Research*

### **Beyza Ecem ÖZ BEDİR**

Department of Medical Biology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

beoz@ybu.edu.tr (mailto:beoz@ybu.edu.tr)

### **Débora DUMMER MEIRA**

Department of Biological Sciences, Nucleus of Human and Molecular Genetics, Federal University of Espirito Santo, Vitória- Espirito Santo, Brazil

debora.dummer.meira@gmail.com (mailto:debora.dummer.meira@gmail.com)

### **Derya ÖZSAVCI**

Department of Biochemistry, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye

derya.ozsavci@marmara.edu.tr (mailto:derya.ozsavci@marmara.edu.tr)

### **Emine TERZİ**

Department of Medical Biology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

emineterzi1990@hotmail.com (mailto:emineterzi1990@hotmail.com)

### **Gülberk UÇAR**

Department of Biochemistry, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye

gulberk@hacettepe.edu.tr (mailto:gulberk@hacettepe.edu.tr)

### **Haidar A ABDULAMIR**

College of Pharmacy, Al-Maaql University, Basra, Iraq

h\_al\_attar@yahoo.com (mailto:h\_al\_attar@yahoo.com)

### **Hamide Sena ÖZBAY**

Department of Biochemistry, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye

senaozbay@hacettepe.edu.tr (mailto:senaozbay@hacettepe.edu.tr)

**Lokman AYAZ**

Department of Biochemistry, Faculty of Pharmacy, Trakya University, Edirne, Türkiye  
lokmanayaz@yahoo.com (mailto:lokmanayaz@yahoo.com)

*Biotechnology***Ali Demir SEZER**

Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
adsezer@marmara.edu.tr (mailto:adsezer@marmara.edu.tr)

**Ammad Ahmad FAROOQI**

Department of Molecular Oncology, Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan  
farooqiammadahmad@gmail.com (mailto:farooqiammadahmad@gmail.com)

**Ceyda EKENTOK ATICI**

Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
ceyda.ekentok@marmara.edu.tr (mailto:ceyda.ekentok@marmara.edu.tr)

**Murat DOĞAN**

Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Cumhuriyet University, Sivas, Türkiye  
mdogan@cumhuriyet.edu.tr (mailto:mdogan@cumhuriyet.edu.tr)

**Uğur KARAGÖZ**

Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Trakya University, Edirne, Türkiye  
ugurkaragoz@trakya.edu.tr (mailto:ugurkaragoz@trakya.edu.tr)

*Clinical Pharmacy & Social Pharmacy & Pharmacoeconomy***Abdikarim Mohammed ABDI**

Department of Clinical Pharmacy, Faculty of Pharmacy, Yeditepe University, Istanbul, Türkiye  
abdikarim.abdi@yeditepe.edu.tr (mailto:abdikarim.abdi@yeditepe.edu.tr)

**Betül OKUYAN**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
betul.okuyan@marmara.edu.tr (mailto:betul.okuyan@marmara.edu.tr)

**Maja ORTNER HADŽIABDIĆ**

Centre for Applied Pharmacy, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

mortner@pharma.hr (mailto:mortner@pharma.hr)

**Mesut SANCAR**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye

mesut.sancar@marmara.edu.tr (mailto:mesut.sancar@marmara.edu.tr)

**Mirela MIRAÇI**

Faculty of Pharmacy, University of Medicine, Tirana, Albania

mirela.miraci@umed.edu.al (mailto:mirela.miraci@umed.edu.al)

**Tarik CATIĆ**

Department of Pharmacy, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

tarik.catic@ssst.edu.ba (mailto:tarik.catic@ssst.edu.ba)

*In Silico Studies***Efe Dođukan DİNCEL**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Istanbul University, Istanbul, Türkiye

efe.dincel@istanbul.edu.tr (mailto:efe.dincel@istanbul.edu.tr)

**Gizem TATAR YILMAZ**

Department of Biostatistics and Medical Informatics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye

gizemtatar@gmail.com (mailto:gizemtatar@gmail.com)

*Medicinal Chemistry***Bahadır BÜLBÜL**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Düzce University, Düzce, Türkiye

bahadir.bulbul@yahoo.com.tr (mailto:bahadir.bulbul@yahoo.com.tr)

**Entela HALOCI**

Faculty of Pharmacy, University of Medicine, Tirana, Albania

entela.haloci@umed.edu.al (mailto:entela.haloci@umed.edu.al)

**Hasan Erdinç SELLİTEPE**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Karadeniz Technical University, Trabzon, Türkiye

esellitepe@ktu.edu.tr (mailto:esellitepe@ktu.edu.tr)

**Kerem BURAN**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Health Sciences, Istanbul, Türkiye  
Kerem.buran@sbu.edu.tr (mailto:Kerem.buran@sbu.edu.tr)

**Simone CARRADORI**

Department of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy  
simone.carradori@unich.it (mailto:simone.carradori@unich.it)

**Somaieh SOLTANI**

Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran  
soltanis@tbzmed.ac.ir (mailto:soltanis@tbzmed.ac.ir)

*Microbiology & Immunology*

**Erkan RAYAMAN**

Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
erayaman@marmara.edu.tr (mailto:erayaman@marmara.edu.tr)

**Gülgün TINAZ**

Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
gulgun.tinaz@marmara.edu.tr (mailto:gulgun.tinaz@marmara.edu.tr)

**Zahraa AMER HASHIM**

Department of Microbiology and Immunology, College of Pharmacy, Mosul University, Mosul, Iraq  
hashimz@uomosul.edu.iq (mailto:hashimz@uomosul.edu.iq)

*Pharmaceutical Botany & Pharmacognosy & Chemistry of Natural Products*

**Ahmet EMİR**

Department of Pharmacognosy, Faculty of Pharmacy, Ege University, Izmir, Türkiye  
ahmet.emir@ege.edu.tr (mailto:ahmet.emir@ege.edu.tr)

**Annalisa CHIAVAROLI**

Department of Pharmacology, Faculty of Pharmacy, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy  
annalisa.chiavaroli@unich.it (mailto:annalisa.chiavaroli@unich.it)

**Antoaneta TREDAFILOVA**

Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria

antoaneta.trendafilova@orgchm.bas.bg (mailto:antoaneta.trendafilova@orgchm.bas.bg)

**Ayşe Esra KARADAĞ**

Department of Pharmacognosy, Faculty of Pharmacy, Istanbul Medipol University, Istanbul, Türkiye  
ayseesraguler@gmail.com (mailto:ayseesraguler@gmail.com)

**Ceren EMİR**

Department of Pharmacognosy, Faculty of Pharmacy, Ege University, Izmir, Türkiye  
ceren.acir@ege.edu.tr (mailto:ceren.acir@ege.edu.tr)

**Claudio FERRANTE**

Department of Pharmacology, Faculty of Pharmacy, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy

claudio.ferrante@unich.it (mailto:claudio.ferrante@unich.it)

**İ. İrem TATLI ÇANKAYA**

Department of Pharmaceutical Botany, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye  
iremcanakaya@gmail.com (mailto:iremcanakaya@gmail.com)

**Laleh KHODAIIE**

Department of Pharmacognosy, Faculty of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

khodaiel@gmail.com (mailto:khodaiel@gmail.com)

**Lejla KLEPO**

Department of Chemistry, Faculty of Science, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

klepolejla@gmail.com (mailto:klepolejla@gmail.com)

**Mirjana MARČETIĆ**

Department of Pharmacognosy, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia  
mirjana.marctic@pharmacy.bg.ac.rs (mailto:mirjana.marctic@pharmacy.bg.ac.rs)

**Nurettin YAYLI**

Department of Pharmacognosy, Faculty of Pharmacy, Karadeniz Technical University, Trabzon, Türkiye

yayli@ktu.edu.tr (mailto:yayli@ktu.edu.tr)

**Patrícia RIJO**

Research Center for Biosciences & Health Technologies, Lusofona University, Lisbon, Portugal  
p1609@ulusofona.pt (mailto:p1609@ulusofona.pt)

*Pharmacognosy*



**Sneha AGRAWAL**

Department of Pharmacognosy, Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai, Maharashtra, India

sneha.agrawal@bvcop.in (mailto:sneha.agrawal@bvcop.in)

**Turgut TAŞKIN**

Department of Pharmacognosy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye

turguttaskin@marmara.edu.tr (mailto:turguttaskin@marmara.edu.tr)

**Viktorija MAKSIMOVA**

Department of Applied Sciences, Faculty of Medical Sciences, Goce Delcev University, Shtip, Republic of N. Macedonia

viktorija.maksimova@ugd.edu.mk (mailto:viktorija.maksimova@ugd.edu.mk)

**Vildan ÇELİKSOY**

School of Optometry and Vision Sciences, Cardiff University, Cardiff, UK

celiksoyv92@gmail.com (mailto:celiksoyv92@gmail.com)

**Vilma TOSKA PAPAJANI**

Department of Pharmacy, University of Medicine, Tirana, Albania

toskavilma@gmail.com (mailto:toskavilma@gmail.com)

**Zoran ZEKOVIĆ**

Faculty of Technology, University of Novi Sad, Novi Sad, Serbia

zzekovic@tf.uns.ac.rs (mailto:zzekovic@tf.uns.ac.rs)

*Pharmaceutics***Afife Büşra UĞUR KAPLAN**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Atatürk University, Erzurum, Türkiye

afife.busra.ugur@gmail.com (mailto:afife.busra.ugur@gmail.com)

**Burcu ÜNER**

Pharmaceutical and Administrative Sciences, The University of Health Science and Pharmacy in St. Louis, USA

uner.burcu@yahoo.com (mailto:uner.burcu@yahoo.com)

**Dhanashree P. SANAP**

Department of Pharmaceutics, Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai, India

dhanashree.sanap@bvcop.in (mailto:dhanashree.sanap@bvcop.in)

**Dinesh KUMAR**

Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (BHU), Varanasi, India

dinesh.phe@itbhu.ac.in (mailto:dinesh.phe@itbhu.ac.in)

**Ebru ALTUNTAŞ**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Istanbul, Türkiye  
ebru.altuntas@istanbul.edu.tr (mailto:ebru.altuntas@istanbul.edu.tr)

**Ela HOTI**

Faculty of Pharmacy, University of Medicine, Tirana, Albania  
ela.hoti@umed.edu.al (mailto:ela.hoti@umed.edu.al)

**Emrah ÖZAKAR**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Atatürk University, Erzurum, Türkiye  
emrahozakar@atauni.edu.tr (mailto:emrahozakar@atauni.edu.tr)

**Enkelejda GOCI**

Pharmacotherapeutic Research Center, Aldent University, Tirana, Albania  
enkelejda.goci@ual.edu.al (mailto:enkelejda.goci@ual.edu.al)

**Kleva SHPATI**

Department of Pharmacy, Albanian University , Tirana, Albania  
k.shpati@albanianuniversity.edu.al (mailto:k.shpati@albanianuniversity.edu.al)

**Sakine TUNCAY TANRIVERDİ**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Ege University, İzmir, Türkiye  
sakine.tuncay@ege.edu.tr (mailto:sakine.tuncay@ege.edu.tr)

**Gülşah GEDİK**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Trakya University, Edirne, Türkiye  
gulsahgedik@trakya.edu.tr (mailto:gulsahgedik@trakya.edu.tr)

**Ongun Mehmet SAKA**

Department of Pharmaceutical Technology and Biotechnology, Faculty of Pharmacy, Ankara University, Ankara, Türkiye  
omsaka@gmail.com (mailto:omsaka@gmail.com)

**Oya KERİMOĞLU**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
osipahigil@marmara.edu.tr (mailto:osipahigil@marmara.edu.tr)

**Pankaj DWIVEDI**

Pharmaceutical and Administrative Sciences, The University of Health Science and Pharmacy in St. Louis, USA  
dwivedipank@gmail.com (mailto:dwivedipank@gmail.com)

**Rezarta SHKRELI**

Department of Pharmacy, Faculty of Medical Sciences, Aldent University, Tirana, Albania  
rezarta.shkreli@ual.edu.al (mailto:rezarta.shkreli@ual.edu.al)

**Renuka KHATIK**

Washington University in St. Louis, USA  
renukadops@gmail.com (mailto:renukadops@gmail.com)

**Rukiye SEVİNÇ ÖZAKAR**

Department of Pharmaceutical Technology, Faculty of Pharmacy, Atatürk University, Erzurum, Türkiye  
rukiyeso@atauni.edu.tr (mailto:rukiyeso@atauni.edu.tr)

**Saeideh SOLTANI**

Novel Drug Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran  
soltanisa@pharm.mui.ac.ir (mailto:soltanisa@pharm.mui.ac.ir)

*Pharmacology & Toxicology***Ana V. PEJČIĆ**

Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia  
anapejic201502@yahoo.com (mailto:anapejic201502@yahoo.com)

**Ayfer BECEREN**

Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
ayfer.tozan@marmara.edu.tr (mailto:ayfer.tozan@marmara.edu.tr)

**Ayşenur GÜNAYDIN AKYILDIZ**

Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Bezmialem Vakıf University, Istanbul, Türkiye

gunaydinaysenur@gmail.com (mailto:gunaydinaysenur@gmail.com)

**Ayça TOPRAK SEMİZ**

Vocational School of Health Services, Giresun University, Giresun, Türkiye

ayca.toprak@giresun.edu.tr (mailto:ayca.toprak@giresun.edu.tr)

**Büşra ERTAŞ**

Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
busra.ertas@marmara.edu.tr (mailto:busra.ertas@marmara.edu.tr)

**Fatiha MISSOUN**

Laboratory of Pharmacognosy and Api-Phytotherapy, University of Mostaganem, Mostaganem, Algeria

fatiha.missoun@univ-mosta.dz (mailto:fatiha.missoun@univ-mosta.dz)

**Klodiola DHAMO**

Faculty of Technical Medical Sciences, Aldent University, Tirana, Albania

klodiola.dhamo@ual.edu.al (mailto:klodiola.dhamo@ual.edu.al)

**Merve KABASAKAL**

Department of Medical Pharmacology, Faculty of Medicine, University of Health Sciences, Istanbul, Türkiye

merve.kabasakal@sbu.edu.tr (mailto:merve.kabasakal@sbu.edu.tr)

**Nurdan TEKİN**

Department of Medical Pharmacology, Faculty of Medicine, University of Health Sciences, Istanbul, Türkiye

nurdan.tekin@sbu.edu.tr (mailto:nurdan.tekin@sbu.edu.tr)

**Rümeysa KELEŞ KAYA**

Department of Medical Pharmacology, Faculty of Medicine, Sakarya University, Sakarya, Türkiye

rumeysakeles@sakarya.edu.tr (mailto:rumeysakeles@sakarya.edu.tr)

**Ünzile YAMAN**

Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Katip Çelebi University, İzmir, Türkiye

unzileyaman@gmail.com (mailto:unzileyaman@gmail.com)

**Zarife Nigar ÖZDEMİR KUMRAL**

Department of Physiology, Faculty of Medicine, Marmara University, Istanbul, Türkiye

znozdemir@marmara.edu.tr (mailto:znozdemir@marmara.edu.tr)

**Zeina ALTHANOON**

Department of Pharmacology and Toxicology, College of Pharmacy, Mosul University, Mosul, Iraq

dr.zeina@uomosul.edu.iq (mailto:dr.zeina@uomosul.edu.iq)

*Copy Editor*

**Ayşe Nur HAZAR YAVUZ**

Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye

ayse.hazar@marmara.edu.tr (mailto:ayse.hazar@marmara.edu.tr)

**Büşra ERGEN**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye

busra.ergen@marmara.edu.tr (mailto:busra.ergen@marmara.edu.tr)

**Elif Beyzanur POLAT**

Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
elif.beyzanur@marmara.edu.tr (mailto:elif.beyzanur@marmara.edu.tr)

**Fatih Taha ÇİFTÇİ**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
fatih.ciftci@marmara.edu.tr (mailto:fatih.ciftci@marmara.edu.tr)

**Müzeyyen AKSOY**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
muzeyyen.aksoy@marmara.edu.tr (mailto:muzeyyen.aksoy@marmara.edu.tr)

**Ömer Faruk ÖZKANLI**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
oozkanli@marmara.edu.tr (mailto:oozkanli@marmara.edu.tr)

**Sinan SERMET**

Faculty of Health Sciences, Istanbul Arel University, Istanbul, Türkiye  
sinan.sermet@gmail.com (mailto:sinan.sermet@gmail.com)

**Şeyma GÖZELİZMİR**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
seyma.gozelizmir@marmara.edu.tr (mailto:seyma.gozelizmir@marmara.edu.tr)

**Yeliz ŞAHİN**

Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye  
yeliz.sahin@marmara.edu.tr (mailto:yeliz.sahin@marmara.edu.tr)

*Language Editor*

**Khadija ALJESRI**

Department of Pharmacology, Institute of Health Sciences, Marmara University, Istanbul, Türkiye

*Biostatistics Editor*

**Gülnaz NURAL BEKİROĞLU**

Department of Bioistatistics, Faculty of Medicine, Marmara University, Istanbul, Türkiye  
nural@marmara.edu.tr (mailto:nural@marmara.edu.tr)

Marmara University

Home (<https://jrespharm.com/>)

Aims and Scope (<static.php?id=1>)

[Editorial Board \(static.php?id=2\)](#)

[Advisory Board \(content.php?id=82\)](#)

[Table of Contents \(static.php?id=4\)](#)

[Author Guidelines \(static.php?id=7\)](#)

[Abstracting / Indexing \(static.php?id=9\)](#)

[Contact \(static.php?id=8\)](#)

---

Other Issues : [◀ Previous \(content.php?id=62\)](#)

[Next ▶ \(content.php?id=64\)](#)

[Issue XML \(issue-xml.php?id=63\)](#)

Journal of Research in

2020 , Vol 24 , Issue 4

Pharmacy

➔ Research Article (16)

Research Article

[Clear](#)

[View Selected Abstracts](#)

**Synthesis, *in silico* studies and cytotoxicity evaluation of novel 1,3,4-oxadiazole derivatives designed as potential mPGES-1 inhibitors (abstract.php?id=826) *Research Article***

*Pages 436-451*

Gizem ERENDOY, Kai DING, Chang-Guo ZHAN, Ammar ELMEZAYEN, Kemal YELEKÇİ, Merve DURACIK, Özlem BİNGÖL ÖZAKPINAR, İlkay KÜÇÜKGÜZEL

DOI : 10.35333/jrp.2020.187

[Abstract \(abstract.php?lang=en&id=826\)](#)

[Full Text PDF \(pdf.php?&id=826\)](#)

[Similar Articles \(similar.php?&id=826\)](#)

[E-mail to Author \(mailto:ikucukguzel@marmara.edu.tr\)](mailto:ikucukguzel@marmara.edu.tr)

[How to Cite \(ajax\\_handler.php?id=826\)](#)

**Novel nitrogen-containing heterocyclic compounds in GPR109A as an anti-hyperlipidemic: Homology modeling, docking, dynamic simulation studies (abstract.php?id=809) *Research Article***

*Pages 452-463*

Prajakta B. KOTHAWADE, Kiran Bharat LOKHANDE, Kakumani Venkateswara SWAMY, Sohan S. CHITLANGE, Asha B. THOMAS

DOI : 10.35333/jrp.2020.193

[Abstract \(abstract.php?lang=en&id=809\)](#)

[Full Text PDF \(pdf.php?&id=809\)](#)

[Similar Articles \(similar.php?&id=809\)](#)

[E-mail to Author \(mailto:asha.thomas@dypvp.edu.in\)](mailto:asha.thomas@dypvp.edu.in)

[How to Cite \(ajax\\_handler.php?id=809\)](#)

**Acetylcholinesterase inhibitory potencies of new pyrazoline derivatives (abstract.php?id=816) *Research Article***

*Pages 464-471*

Mehtap TUĞRAK, Halise İnci GÜL, İlhami GÜLÇİN

DOI : 10.35333/jrp.2020.194

[Abstract \(abstract.php?lang=en&id=816\)](#)

[Full Text PDF \(pdf.php?&id=816\)](#)

[Similar Articles \(similar.php?&id=816\)](#)

[E-mail to Author \(mailto:incigul1967@yahoo.com\)](mailto:incigul1967@yahoo.com)

[How to Cite \(ajax\\_handler.php?id=816\)](#)

**Evaluation of cholinesterase inhibitory activity of six Indonesian Cassia species (abstract.php?id=820) *Research Article***

*Pages 472-478*

Suciati SUCIATI, Erlinda Rhoematul LAILI, Debora POERWANTORO, Anita Probo HAPSARI, Lailatul Zakiyah

GIFANDA, Karma RABGAY, Wiwied EKASARI, Kornkanok INGGANINAN



DOI : 10.35333/jrp.2020.195

[Abstract \(abstract.php?lang=en&id=820\)](#)

[Full Text PDF \(pdf.php?&id=820\)](#)

[Similar Articles \(similar.php?&id=820\)](#)

[E-mail to Author \(mailto:suciati@ff.unair.ac.id\)](mailto:suciati@ff.unair.ac.id)

[How to Cite \(ajax\\_handler.php?id=820\)](#)

**In vitro antihepatocellular carcinoma activity of secondary metabolites of *Centaurea kilaea* Boiss (abstract.php?id=822) *Research Article***

*Pages 479-486*

Turgut ŞEKERLER, Ali ŞEN, Leyla BİTİŞ, Azize ŞENER

DOI : 10.35333/jrp.2020.196

[Abstract \(abstract.php?lang=en&id=822\)](#)

[Full Text PDF \(pdf.php?&id=822\)](#)

[Similar Articles \(similar.php?&id=822\)](#)

[E-mail to Author \(mailto:turgut.sekerler@marmara.edu.tr\)](mailto:turgut.sekerler@marmara.edu.tr)

[How to Cite \(ajax\\_handler.php?id=822\)](#)

**Quantification of phenolic and flavonoid contents and some biological activities of *Ornithogalum sigmoideum* Freyn & Sint (abstract.php?id=825) *Research Article***

*Pages 487-496*

Can Özgür YALÇIN, Sezen YILMAZ SARIALTIN, Derya ÇİÇEK POLAT

DOI : 10.35333/jrp.2020.197

[Abstract \(abstract.php?lang=en&id=825\)](#)

[Full Text PDF \(pdf.php?&id=825\)](#)

[Similar Articles \(similar.php?&id=825\)](#)

[E-mail to Author \(mailto:sezen.yilmaz@ankara.edu.tr\)](mailto:sezen.yilmaz@ankara.edu.tr)

[How to Cite \(ajax\\_handler.php?id=825\)](#)

**Evaluation of phenolic compounds and protective effects of olive (*Olea europaea* L.) leaf extracts on endothelial cells against hydrogen peroxide-induced toxicity (abstract.php?id=824) *Research Article***

*Pages 497-507*

Hilal TORUL, Nurgün KÜÇÜKBOYACI, Uğur TAMER, Çimen KARASU

DOI : 10.35333/jrp.2020.198

[Abstract \(abstract.php?lang=en&id=824\)](#)

[Full Text PDF \(pdf.php?&id=824\)](#)

[Similar Articles \(similar.php?&id=824\)](#)

[E-mail to Author \(mailto:hilaltorul@gazi.edu.tr\)](mailto:hilaltorul@gazi.edu.tr)

[How to Cite \(ajax\\_handler.php?id=824\)](#)

**Protective effect of *Caesalpinia sappan* L. extract against H<sub>2</sub>O<sub>2</sub>-induced oxidative stress on HaCaT and its formulation as antioxidant cream (abstract.php?id=819) *Research Article***

*Pages 508-517*

Leonny Yulita HARTIADI, Agnes Anania Triavika SAHAMASTUTI

DOI : 10.35333/jrp.2020.199

[Abstract \(abstract.php?lang=en&id=819\)](#)

[Full Text PDF \(pdf.php?&id=819\)](#)

[Similar Articles \(similar.php?&id=819\)](#)

[E-mail to Author \(mailto:leonny.hartiadi@i3l.ac.id\)](mailto:leonny.hartiadi@i3l.ac.id)

[How to Cite \(ajax\\_handler.php?id=819\)](#)

**Thin layer chromatography as a simple and quick in-process tool for qualitative and semi-quantitative determination of unentrapped drugs in liposomal formulations**

**(abstract.php?id=823) Research Article**

*Pages 518-528*

Mukesh KUMAR, Swaroop Rameshwarji LAHOTI

DOI : 10.35333/jrp.2020.200

[Abstract \(abstract.php?lang=en&id=823\)](#)

[Full Text PDF \(pdf.php?&id=823\)](#)

[Similar Articles \(similar.php?&id=823\)](#)

[E-mail to Author \(mailto:mukeshk32@hotmail.com\)](mailto:mukeshk32@hotmail.com)

[How to Cite \(ajax\\_handler.php?id=823\)](#)

**Formulation and optimization of gellan gum-poloxamer based dexamethasone mucoadhesive in situ gel (abstract.php?id=821) Research Article**

*Pages 529-538*

Seda RENÇBER, Sinem Yaprak KARAVANA

DOI: 10.35333/jrp.2020.201

[Abstract \(abstract.php?lang=en&id=821\)](#)

[Full Text PDF \(pdf.php?&id=821\)](#)

[Similar Articles \(similar.php?&id=821\)](#)

[E-mail to Author \(mailto:seda.rencber@ikc.edu.tr\)](mailto:seda.rencber@ikc.edu.tr)

[How to Cite \(ajax\\_handler.php?id=821\)](#)

**Formulation and pharmacokinetic evaluation of rifampicin solid lipid nanoparticles (abstract.php?id=817) *Research Article***

*Pages 539-551*

Ahmed GARDOUH, Alshimaa GAMAL, Shadeed GAD

DOI: 10.35333/jrp.2020.202

[Abstract \(abstract.php?lang=en&id=817\)](#)

[Full Text PDF \(pdf.php?&id=817\)](#)

[Similar Articles \(similar.php?&id=817\)](#)

[E-mail to Author \(mailto:ahmed\\_mahmoud@pharm.suez.edu.eg\)](mailto:ahmed_mahmoud@pharm.suez.edu.eg)

[How to Cite \(ajax\\_handler.php?id=817\)](#)

**Dolutegravir sodium loaded solid lipid nanoparticles: A vaginal drug delivery system for pre-exposure prophylaxis of HIV (abstract.php?id=818) *Research Article***

*Pages 552-561*

Ruhi ANJUM, PK LAKSHMI

DOI: 10.35333/jrp.2020.203

[Abstract \(abstract.php?lang=en&id=818\)](#)

[Full Text PDF \(pdf.php?&id=818\)](#)

[Similar Articles \(similar.php?&id=818\)](#)

[E-mail to Author \(mailto:drlakshmisuresh@gmail.com\)](mailto:drlakshmisuresh@gmail.com)

[How to Cite \(ajax\\_handler.php?id=818\)](#)

**Formulation and evaluation of fluvastatin sodium drug-in-adhesive transdermal system (abstract.php?id=802) *Research Article***

*Pages 562-571*

Rachel GEEVARGHESE, Satish SHIROLKAR

DOI : 10.35333/jrp.2020.204

[Abstract \(abstract.php?lang=en&id=802\)](#)

[Full Text PDF \(pdf.php?&id=802\)](#)

[Similar Articles \(similar.php?&id=802\)](#)

[E-mail to Author \(mailto:rachel\\_hvl@yahoo.co.in\)](mailto:rachel_hvl@yahoo.co.in)

[How to Cite \(ajax\\_handler.php?id=802\)](#)

**Development of a multiple-unit system: Tablets containing amlodipine besylate which have different release kinetics (abstract.php?id=815) *Research Article***

*Pages 572-581*

Ozan TEKDEMİR, Gizem TILKI, Timuçin UĞURLU

DOI : 10.35333/jrp.2020.205

[Abstract \(abstract.php?lang=en&id=815\)](#)

[Full Text PDF \(pdf.php?&id=815\)](#)

[Similar Articles \(similar.php?&id=815\)](#)

[E-mail to Author \(mailto:tugurlu@marmara.edu.tr\)](mailto:tugurlu@marmara.edu.tr)

[How to Cite \(ajax\\_handler.php?id=815\)](#)

**Evaluation of regular UPLC/MS system for experimental and clinical proteomics**

**(abstract.php?id=813) Research Article**

*Pages 582-592*

Engin KOÇAK, Sacide ALTINÖZ

DOI : 10.35333/jrp.2020.206

[Abstract \(abstract.php?lang=en&id=813\)](#)

[Full Text PDF \(pdf.php?&id=813\)](#)

[Similar Articles \(similar.php?&id=813\)](#)

[E-mail to Author \(mailto:saltinoz@hacettepe.edu.tr\)](mailto:saltinoz@hacettepe.edu.tr)

[How to Cite \(ajax\\_handler.php?id=813\)](#)

**Metabolic response of Escherichia coli to subinhibitory concentration of ofloxacin**

**(abstract.php?id=814) Research Article**

*Pages 593-601*

Engin KOÇAK, Ceren ÖZKUL

DOI : 10.35333/jrp.2020.207

[Abstract \(abstract.php?lang=en&id=814\)](#)

[Full Text PDF \(pdf.php?&id=814\)](#)

[Similar Articles \(similar.php?&id=814\)](#)

[E-mail to Author \(mailto:kengin@hacettepe.edu.tr\)](mailto:kengin@hacettepe.edu.tr)

[How to Cite \(ajax\\_handler.php?id=814\)](#)

---

Marmara University

[Home \(https://jrespharm.com/\)](https://jrespharm.com/)

[Aims and Scope \(static.php?id=1\)](#)

[Editorial Board \(static.php?id=2\)](#)

[Advisory Board \(content.php?id=82\)](#)

[Table of Contents \(static.php?id=4\)](#)









[Author Guidelines \(static.php?id=7\)](#)

[Abstracting / Indexing \(static.php?id=9\)](#)

[Contact \(static.php?id=8\)](#)

---

# Evaluation of cholinesterase inhibitory activity of six Indonesian *Cassia* species

Suciati SUCIATI <sup>1,2,\*</sup> , Erlinda Rhoematul LAILI <sup>1</sup> , Debora POERWANTORO <sup>1</sup> ,  
Anita Probo HAPSARI <sup>1</sup> , Lailatul Zakiyah GIFANDA <sup>1</sup> , Karma RABGAY <sup>3</sup> ,  
Wiwied EKASARI <sup>1</sup> , Kornkanok INGGANINAN <sup>1,3</sup> 

<sup>1</sup> Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, East Java, Indonesia.

<sup>2</sup> Center for Natural Product Medicine Research and Development, Institute of Tropical Diseases, Universitas Airlangga, Surabaya 60115, East Java, Indonesia.

<sup>3</sup> Bioscreening Unit, Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmaceutical Sciences and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok, Thailand

\* Corresponding Author. suciati@ff.unair.ac.id (S.); Tel. +62-31-593 31 50.

Received: 18 December 2019 / Revised: 12 May 2020 / Accepted: 01 June 2020

**ABSTRACT:** Alzheimer's disease (AD) is a neurodegenerative disorder, which is the most common cause of dementia. The aging population means that the number of people suffering from AD is expected to increase each year if there is no effective treatment found. One of the strategies for the treatment of AD is the use of cholinesterase inhibitors. Plants have been the source of many bioactive metabolites, including cholinesterase inhibitors. The objective of this study is to investigate the potency of several plant extracts from the genus *Cassia* as cholinesterase inhibitors. The cholinesterase inhibitory screening was carried out against two enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), according to the modified Ellman's method. The chemistry of the active fractions was studied by LC-MS/MS method. The results suggested that amongst six plant extracts from the genus *Cassia* investigated, the ethanolic extract of *Cassia spectabilis* showed the strongest inhibition against both AChE and BChE enzymes, with IC<sub>50</sub> values of 39.5 and 36.9 µg/mL, respectively. Investigation on the *n*-hexane, ethyl acetate, and *n*-butanol fractions obtained from the *C. spectabilis* extract showed that the ethyl acetate and the *n*-butanol fractions gave better inhibitory activity compared to the *n*-hexane fraction. Based on the LC-MS/MS data, the two active fractions gave similar profile. Both fractions contained alkaloid cassine and spectraline, which may responsible for the cholinesterase inhibitory activity.

**KEYWORDS:** Cholinesterase inhibitor; Alzheimer's disease ; *Cassia* species; *Cassia spectabilis*.

## 1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is the most common cause of dementia [1]. The manifestation of this disease includes irreversible memory and cognitive deficiency. The common feature of this disease is the low level of the neurotransmitter acetylcholine in the brain due to loss of cholinergic nerves as well as the presence of senile plaques and neurofibrillary tangles which can destroy the neurons [1,2]. This disease commonly occurs in elderly ages, and the onset mostly appears in the mid 60's population [1]. The increase in life expectancy means that the number of people suffering from AD is anticipated to increase each year if there is no effective treatment found.

As cholinergic deficiency is the common feature of AD, one of the treatments for this disease is the use of acetylcholinesterase (AChE) inhibitor, such as tacrine, donepezil, rivastigmine, and galantamine. Tacrine and donepezil are both synthetic compounds, while rivastigmine is a derivative developed from natural compound physostigmine [3]. Galantamine is an AChE inhibitor derived from natural sources. It is an alkaloid which first isolated from the snowdrop *Galanthus nivalis* (Amaryllidaceae) [4]. Studies have shown that these compounds gave benefits on cognitive, functional and behavioral effects on AD patients, however, several side effects and limited effectiveness have also been reported [5,6]. Another natural product that has

**How to cite this article:** Suciati, Laili ER, Poerwantoro D, Hapsari AP, Gifanda LZ, Rabgay K, Ekasari W, Ingganinan K. Evaluation of cholinesterase inhibitory activity of six Indonesian *Cassia* species. J Res Pharm. 2020; 24(4): 472-478.



been studied thoroughly as AChE inhibitor is a sesquiterpene alkaloid, Huperzine A, obtained from *Huperzia* spp. The product containing extract of *Huperzia* spp has been commercialized as a food supplement for memory support in China [2].

Considering the two AChE inhibitors above are natural origin, research on finding either new or more effective compounds has been a target of many researchers. Recently we have reported the potency of several marine sponges as acetylcholinesterase inhibitor [7]. In the present study investigation of *Cassia* spp as cholinesterase inhibitor was carried out. The genus *Cassia* in the family Caesalpiniaceae have been known as flowering plants which comprising of more than 500 species, and are distributed widely in the tropical and subtropical regions [8-10]. *Cassia* spp are usually grown as ornamental plants, but many of these plants have great economic importance as well as its utilization in traditional medicine. The leave and the bark of *Cassia fistula* have been used to treat blackwater fever as well as a laxative [8]. Other traditional usages of *Cassia* spp have also been documented, such as for gastrointestinal problems, skin diseases, cough, bronchitis and cardiac disorders [10,11]. Metabolites reported from *Cassia* species include anthraquinones, terpenoids, xanthenes, flavonoids as well as alkaloids. Many of these compounds posses promising biological activities, such as antioxidant, anti-inflammatory, anticancer, antiplasmodial, and hepatoprotective agents [11-14]. Anti-AD activity was reported from *Cassia obtusifolia*; the seeds extract of this plant can improve memory and learning in mice [15], as well as ameliorates amyloid  $\beta$ -induced synaptic dysfunction through anti-inflammatory and Akt/GSK-3 $\beta$  pathways [16]. *C. obtusifolia* extract was also found to inhibit AChE, BChE, and BACE1 ( $\beta$ -site amyloid precursor protein cleaving enzyme 1) [17]. It was suggested that the naphopyrone compounds may be responsible for these activities [18]. Freitas *et al.* (2011) have reported that the extract of *Cassia alata* leaves has shown AChE inhibition [19]. Based on these reports, the potency of other *Cassia* species as cholinesterase inhibitors is worth to be investigated.

## 2. RESULTS AND DISCUSSION

### 2.1. Cholinesterase inhibitory assay

The ethanolic extracts were prepared from the leaves of six species of the genus *Cassia*, namely *Cassia spectabilis* L. (Syn. *Senna spectabilis* L.), *Cassia javanica* L., *Cassia grandis* L.f, *Cassia moschata* Kunth, *Cassia fistula* L., and *Cassia siamea* Lam.(Syn. *Senna siamea* (Lam.) H.S. Irwin & Barneby. The samples were screened against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes at a concentration of 100  $\mu$ g/mL. The results as can be seen in Figure 1 suggested that the highest inhibition against both enzymes was given by *C. spectabilis* and the lowest inhibition was shown by *C. fistula* extract. The inhibitory activity of *C. spectabilis* extract was higher against BChE (85.2%) compared to that against AChE enzyme (53.8%). The *C. spectabilis* extract was further partitioned with, *n*-hexane, ethyl acetate, and *n*-butanol, sequentially. Each of the fractions was then subjected to cholinesterase inhibitory assay against both AChE and BChE enzymes. The results presented in Figure 2 indicated that the ethyl acetate and the *n*-butanol fractions gave higher inhibition against both enzymes, which suggested that the active compounds are possibly semipolar to polar compounds.

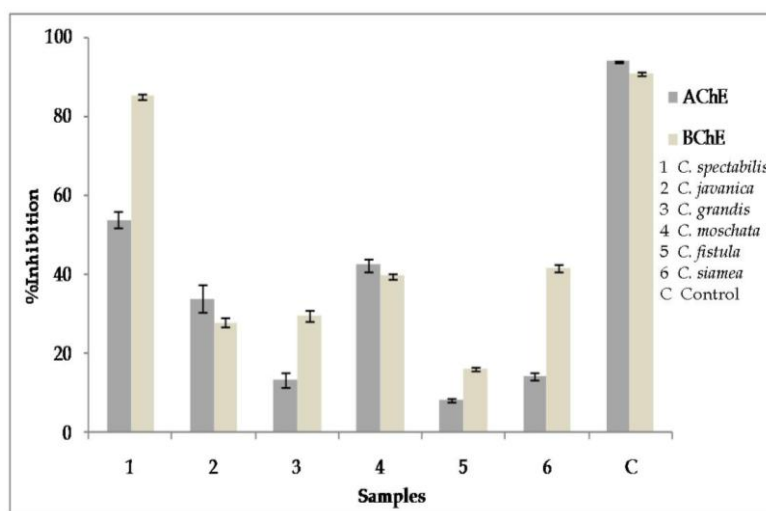


Figure 1. %Inhibition of *Cassia* spp extracts and control (galantamine) against AChE and BChE.

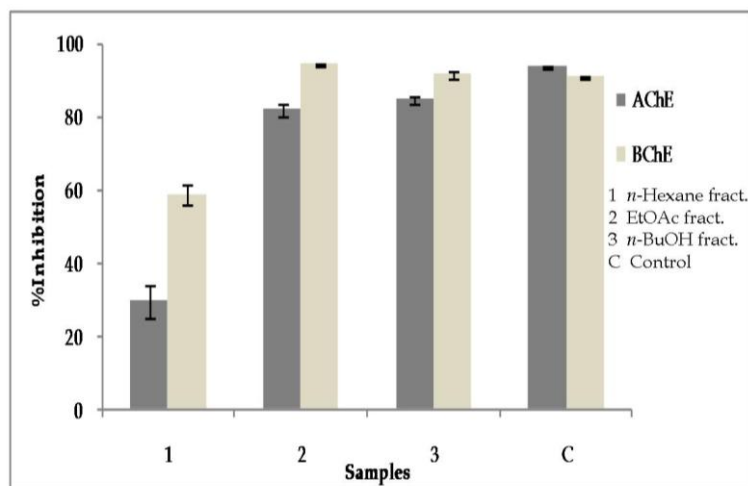


Figure 2. %Inhibition of *C. spectabilis* fractions and control (galantamine) against AChE and BChE.

The 50% inhibitory activities of the ethanolic extract as well as the ethyl acetate and *n*-butanol fractions of *C. spectabilis* were also investigated. The results given in Table 1 show that all samples tested except galantamine exhibited lower IC<sub>50</sub> values against BChE compare to AChE. The lowest IC<sub>50</sub> value was given by the ethyl acetate fraction of *C. spectabilis* at 10.8 and 4.7 μg/mL against AChE and BChE, respectively.

Table 1. The IC<sub>50</sub> *C. spectabilis* extract and fractions.

Samples	IC <sub>50</sub> (μg/mL) <sup>a</sup>	
	AChE	BChE
Ethanol extract	39.5 ± 2.2	36.9 ± 5.1
Ethyl acetate fraction	10.8 ± 0.2	4.7 ± 0.1
<i>n</i> -Butanol fraction	12.8 ± 0.9	10.2 ± 0.9
Galantamine	0.4 ± 0.1	2.2 ± 0.3

<sup>a</sup> Data presented as mean ± SD of three experiments, each done in triplicate.

The ethanolic extract of *C. spectabilis* was subjected to enzyme inhibiting kinetics study, and a Michaelis-Menten plot was determined (Figure 3). The Km value of the substrate ATCI (control) for AChE was 68.4 μM and Vmax was 99.1 μM/min. When the ethanolic extract of *C. spectabilis* leaves was added the Km and Vmax were 62.9 μM and 74.7 μM/min, respectively. There was no significant change in the Km values; indicated that the ethanolic extract of *C. spectabilis* inhibited AChE enzyme in a non-competitive way.

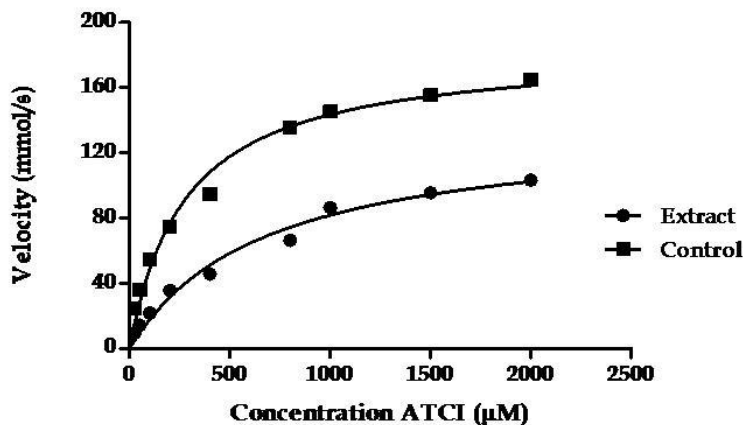
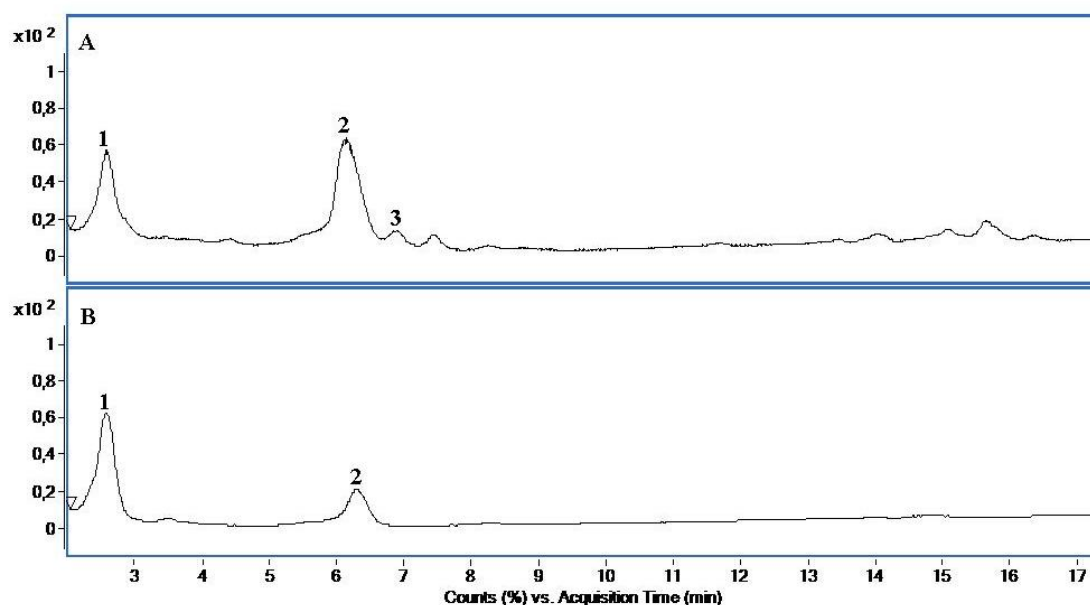


Figure 3. Michaelis-Menten plot of AChE inhibition of *C. spectabilis* extract.

## 2.2. Identification of metabolites by LC-MS/MS

The chemistry of the ethyl acetate and the *n*-butanol fractions were studied by using LC-MS/MS instruments. The total ion chromatograms (TIC) of the two fractions were compared (Figure 4), which showed a similar TIC profile. Both fractions exhibited 2 major peaks at RT 2.57 (1) and 6.14 (2) mins, however, the ethyl acetate fraction also gave several minor peaks at RT approximately 6.9 – 17.9 mins which was not seen in the *n*-butanol fraction. Based on the MS/MS data (Table 2) and comparison to the literature, the two major peaks were identified as cassine (1) and spectraline (2) (Figure 5) [20,21]. In the ethyl acetate fraction, a peak at RT 6.95 mins was observed, which was identified as 3-*O*-acetylspectraline (3). However, other minor peaks can not be identified unambiguously. Cassine and spectraline are two major piperidine alkaloids that have been reported from several parts of *C. spectabilis*, such as from the leaves and flowers [11, 22-24]. Piperidine alkaloids, such as iso-6-cassine and iso-6-spectraline, isolated from *C. spectabilis* have shown potency as depressant and anticonvulsant agents [25,26]. Viegas *et al.* (2005) and Castro *et al.* (2008) have developed semisynthetic derivatives from (-) spectraline isolated from the flower of *C. spectabilis*, the compounds exhibited inhibition against rat brain cholinesterase [27,28]. Freitas *et al.* (2018) have reported that the chloridrate form of cassine, spectraline, and 3-*O*-acetylspectraline demonstrated acetylcholinesterase inhibitory activity [21]. Based on the findings, it is possible that the cholinesterase inhibitory activity in the ethyl acetate and the *n*-butanol fractions of *C. spectabilis* corresponded to the presence of cassine, spectraline, and 3-*O*-acetylspectraline.



**Figure 4.** Total Ion Chromatograms (TIC) of the ethyl acetate (A) and *n*-butanol (B) fractions of *C. spectabilis*.

**Table 2.** LC-MS/MS data for identified alkaloids (1-3) from *C. spectabilis* extract.

Compounds	RT (mins)	[M+H] <sup>+</sup> (m/z)	Product ions m/z (relative abundance) <sup>a</sup>	Formula	Exact mass	Mass error (ppm)
1	2.62	298.2730	280.2625 (100), 210.1841 (3.2), 198.1848 (4.1), 123.1168 (5.3), 109.1014 (45.6)	C <sub>18</sub> H <sub>35</sub> NO <sub>2</sub>	298.2741	-3.69
2	6.22	326.3050	308.2931 (100), 280.2631 (4.7), 240.2335 (1.0), 226.2181 (3.6), 123.1165 (5.4), 109.1012 (21.8)	C <sub>20</sub> H <sub>39</sub> NO <sub>2</sub>	326.3054	-1.23
3	6.95	368.3155	308.2942 (100), 280.2630 (2.4), 240.2343 (2.6), 226.2149 (3.0), 123.1166 (3.3), 109.1005 (17.2)	C <sub>22</sub> H <sub>41</sub> NO <sub>3</sub>	368.3159	-1.09

<sup>a</sup> Product ions at collision energy 40 eV

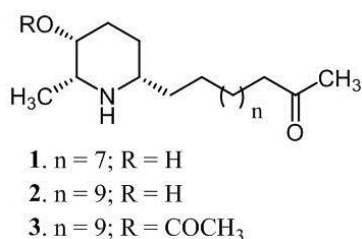


Figure 5. Structures of identified compounds (1-3) from *C. spectabilis*.

### 3. CONCLUSION

Based on these results, the ethanolic extract of *Cassia spectabilis* showed the strongest inhibition against both AChE and BChE enzymes amongst *Cassia* species tested. Further fractionation on *C. spectabilis* extract suggested that the ethyl acetate and the *n*-butanol fractions gave better inhibitory activities compared to the *n*-hexane fraction. Piperidine alkaloids, cassine, spectraline and 3-*O*-acetylspectraline which were identified in the active fractions, may contribute to the cholinesterase inhibitory activity of *C. spectabilis*.

### 4. MATERIALS AND METHODS

#### 4.1. Reagents

Acetylcholinesterase from electric eel (AChE type VI-S), human recombinant acetylcholinesterase (hrAChE), horse-serum butyrylcholinesterase (BChE), acetylthiocholine iodide (ATCI), butyrylthiocholine iodide (BTCI), 5,5'-dithiobis[2-nitrobenzoic acid] (DTNB), and bovine serum albumin (BSA), tris buffer, and galantamine were obtained from Sigma-Aldrich.

#### 4.2. Plant collection, extraction and fractionation

Plant materials were collected from Purwodadi Botanic Garden, East Java, Indonesia on March 9<sup>th</sup>, 2019. Sample specimens (Voucher numbers: PWD 01 - PWD 06) were kept at the Institute of Tropical Diseases Universitas Airlangga. The identification of plant materials was conducted by Purwodadi Botanic Garden (Identification letter number: 0371/IPH.06/HM/III/2019).

The leaves were air-dried for seven days at room temperature followed by grinding to obtain powdered materials. Ten grams of each samples were extracted with ethanol by using ultrasonic extraction for 3 x 10 mins, then the residue and filtrate were separated by filtration. The residue was re-extracted with ethanol using the same procedure for 3 times. The collected filtrate was then concentrated in *vacuo* to yield the crude ethanolic extracts (0.5 - 2.0 g). The ethanolic extract of *C. spectabilis* (0.5 g) was dissolved with a mixture of ethanol and H<sub>2</sub>O (1:1) (20 mL), then further separated by a liquid-liquid partition with *n*-hexane (15 mL), ethyl acetate (15 mL), and followed by *n*-butanol (15 mL). Fractionation with each solvent was conducted 3 times. Each of the fractions obtained was evaporated in *vacuo*, and yielded *n*-hexane (46.9 mg), ethyl acetate (184.4 mg), and *n*-butanol (97.2 mg) fractions.

#### 4.3. Cholinesterase inhibitory assay

The assay was carried out according to the modified Ellman's method [7,29-31]. Plant extracts were dissolved in methanol to make 10 mg/mL concentration, and was serially diluted with 50 mM Tris buffer to obtain a 1 mg/mL concentration containing not more than 10% of methanol. These samples were further diluted in the microplate well to a final test concentration of 100 µg/mL. Sample solutions were added to a 96-well microplate, followed by the addition of 1.5 mM ATCI or 1.5 mM BTCI (25 µL), 3 mM DTNB (125 µL), and Tris buffer (50 µL). The substrate was then hydrolyzed by the addition of 25 µL of 0.22 U/mL of either *Ee*AChE, *hr*AChE or BChE. The solutions were shaken for 30 s in a microplate reader (Bio-Tek Instrument, USA) before measurement. The product, 5-thio-2-nitrobenzoate, indicated by a yellow color was measured at 405 nm every 5 s for 2 min. Every experiment was carried out in triplicates. Galantamine (100 µL) was used as a positive control, and 10% methanol was used as a negative control. For the measurement of IC<sub>50</sub>, serial concentrations of the samples were prepared. The inhibitory activity was calculated as: % Inhibition = [(Mean velocity of control - Mean velocity of sample) / Mean velocity of control] x 100.

#### 4.4. Identification of Metabolites by LC-MS/MS

Identification of metabolites was conducted by using Agilent 1260 Infinity Series HPLC system with an auto-sampler fitted with analytical C-18 column Agilent Poroshell 120 (Agilent Technologies, Santa Clara, CA, USA). The HPLC was connected with an Agilent 6530 UHD Accurate-Mass Q-TOF LC/MS (Agilent Technologies), equipped with dual electrospray ionization (ESI). Samples were dissolved in methanol, and 10  $\mu$ L of samples were injected into the system employing gradient elution of 40-100% methanol/H<sub>2</sub>O containing 0.1% v/v formic acid for 30 mins, flowrate 0.25 mL/min. N<sub>2</sub> was employed as drying gas at a flowrate of 10 L/min. The temperature of the nebulizer was set at 325°C, and the potential of the capillary was 3.5 kV. Positive mode was used and the scan mass range was 100-1000. The MS/MS collision energies were set at 10, 20, and 40 eV. The mass spectrometry data was analyzed using Agilent Mass Hunter Qualitative Analysis software version B06.00.

**Acknowledgements:** Authors acknowledge Faculty of Pharmacy, Universitas Airlangga for BOPTN research grant. Authors acknowledge the Ministry of Research, Technology, and Higher Education of the Republic of Indonesia for research grant PDUPT 2019. This work was also supported by the Thailand Research Fund [IRN61W0005], and the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Ministry of Higher Education, Science, Research and Innovation, Thailand.

**Author contributions:** Concept - S.; Design - S., K.I.; Supervision -S. W.E., K.I.; Resources - S., K.I.; Materials - S., W.E., K.I.; Data Collection and/or Processing - E.R.L., D.P., A.P.H., L.Z.G., K.R.; Analysis and/or Interpretation - S., E.R.L., D.P., A.P.H., L.Z.G., K.R.; Literature Search - S., E.R.L., D.P., A.P.H., L.Z.G., K.R.; Writing - S.; Critical Reviews - S., E.R.L., D.P., A.P.H., L.Z.G., K.R., W.E., K.I.

**Conflict of interest statement:** The authors declared no conflict of interest

#### REFERENCES

- [1] Bird TD. Genetic Aspects of Alzheimer Disease. *Genet Med.* 2008; 10(4): 231-239. [\[CrossRef\]](#)
- [2] Murray AP, Faraoni MB, Castro MJ, Alza NP, Cavallaro V. Natural AChE Inhibitors from Plants and Their Contribution to Alzheimer's Disease Therapy. *Curr Neuropharmacol.* 2013; 11(4): 388-413. [\[CrossRef\]](#)
- [3] Mathew M, Subramanian S. *In Vitro* Screening for Anti-cholinesterase and Antioxidant Activity of Methanolic Extracts of Ayurvedic Medicinal Plants Used for Cognitive Disorders. *Plos one.* 2014; 9(1): e86804. [\[CrossRef\]](#)
- [4] Hostettmann K, Borloz A, Urbain A, Marston A. Natural Product Inhibitors of Acetylcholinesterase. *Curr Org Chem.* 2006; 10(8): 825-847. [\[CrossRef\]](#)
- [5] Lleo A, Greenberg SM, Growdon JH. Current Pharmacotherapy for Alzheimer's Disease. *Annu Rev Med.* 2006; 57: 513-533. [\[CrossRef\]](#)
- [6] Chopra K, Misra S, Kuhad A. Current Perspectives on Pharmacotherapy of Alzheimer's Disease. *Expert Opin Pharmacother.* 2011; 12(3): 335-350. [\[CrossRef\]](#)
- [7] Suciati, Rabgay K, Fachrunniza Y, Saesong T, Hadi TA, Wahyuni TS, Widyawaruyanti A, Ingkaninan K. Enzyme Inhibitory Activities of Marine Sponges against Cholinesterase and 5 $\alpha$ -Reductase. *Malays Appl Biol.* 2019; 48(3): 77-83.
- [8] Ganapaty S, Thomas PS, Ramana KV, Vidyadhar KN, Chakradhar V. A Review of Phytochemical Studies of *Cassia* Species. *Journal of Natural Remedies.* 2002; 2(2): 102-120.
- [9] Dave H, Ledwani L. A Review on Anthraquinones Isolated from *Cassia* Species and Their Applications. *Indian J Nat Prod Resour.* 2012; 3(3): 291-319.
- [10] Sundaramoorthy S, Gunasekaran S, Arunachalam S, Sathivelu M. A Phytopharmacological Review on *Cassia* Species. *J Pharm Sci Res.* 2016; 8(5): 260-264.
- [11] Jothy SL, Torey A, Darah I, Choong YS, Saravanan D, Chen Y, Latha LY, Deivanai S, Sasidharan S. *Cassia spectabilis* (DC) Irwin et Barn: A Promising Traditional Herb in Health Improvement. *Molecules.* 2012; 17(9): 10292-10305. [\[CrossRef\]](#)
- [12] Torey A, Sasidharan S, Yeng C, Latha LY. Standardization of *Cassia spectabilis* with Respect to Authenticity, Assay and Chemical Constituents Analysis. *Molecules.* 2010; 15(5): 3411-3420. [\[CrossRef\]](#)

- [13] Deshpande HA, Bhalsing SR. Recent Advances in the Phytochemistry of Some medicinally important *Cassia* species: A Review. *Int J Pharm Med Bio Sc.* 2013; 2(3): 60-78.
- [14] Ekasari W, Wahyuni TS, Arwaty H, Putri NT. Determination of Effective Dose of Antimalarial from *Cassia spectabilis* Leaf Ethanol Extract in *Plasmodium berghei*-Infected Mice. *Aft J Infect Dis.* 2018; 12(1 Suppl): 110-115.
- [15] Kim DH, Yoon BH, Kim YW, Lee S, Shin BY, Jung JW, Kim HJ, Lee YS, Choi JS, Kim SY, Lee KT, Ryu JH. The Seed Extract of *Cassia obtusifolia* Ameliorates Learning and Memory Impairments Induced by Scopolamine or Transient Cerebral Hypoperfusion in Mice. *J Pharmacol Sci.* 2007; 105(1): 82-93. [CrossRef]
- [16] Yi JH, Park HJ, Lee S, Jung JW, Kim BC, Lee YC, Ryu JH, Kim DH. *Cassia obtusifolia* Seed Ameliorates Amyloid  $\beta$ -Induced Synaptic Dysfunction through Anti-inflammatory and Akt/GSK-3 $\beta$  Pathways. *J Ethnopharmacol.* 2016; 178: 50-57. [CrossRef]
- [17] Jung HA, Ali MY, Jung HJ, Jeong HO, Chung HY, Choi JS. Inhibitory Activities of Major Anthraquinones and Other Constituents from *Cassia obtusifolia* against  $\beta$ -Secretase and Cholinesterases. *J Ethnopharmacol.* 2016; 191: 152-160. [CrossRef]
- [18] Shresta S, Seong SH, Paudel P, Jung HA, Choi JS. Structure Related Inhibition of Enzyme Systems in Cholinesterases and BACE1 *In Vitro* by Naturally Occurring Naphthopyrone and Its Glycosides Isolated from *Cassia obtusifolia*. *Molecules.* 2017; 23(1): 69-86. [CrossRef]
- [19] Feitosa CM, Freitas RM, Luz NN, Bezerra MZ, Trevisan MT. Acetylcholinesterase Inhibition by Some Promising Brazilian Medicinal Plants. *Braz J Biol.* 2011; 71(3): 783-789. [CrossRef]
- [20] Pivatto M, Crotti AEM, Castro-Gamboa I, de Rezende A, Viegas C Jr, Young MCM, Furlan M, Bolzani VS. Electrospray Ionization Mass Spectrometry Screening of Piperidine Alkaloids from *Senna spectabilis* (Fabaceae) Extracts: Fast Identification of New Constituents and Co-metabolites. *J Braz Chem Soc.* 2005; 16(n-6b): 1431-1438. [CrossRef]
- [21] Freitas TR, Danuello A, Viegas C Jr, Bolzani VS, Pivatto M. Mass Spectrometry for Characterization of Homologous Piperidine Alkaloids and Their Activity as Acetylcholinesterase Inhibitors. *Rapid Commun Mass Spectrom.* 2018; 32(15): 1303-1310. [CrossRef]
- [22] Christofidis I, Welter A, Jadot J. Spectaline and Iso-6-cassine, Two New Piperidin 3-ol Alkaloids from The Leaves of *Cassia spectabilis*. *Tetrahedron.* 1977; 33(9): 977-979. [CrossRef]
- [23] Viegas C Jr, Bolzani VS, Furlan M, Berreiro EJ, Young CM, Tomazela D, Eberlin MN. Further Bioactive Piperidine Alkaloids from the Flower and Green Fruits of *Cassia spectabilis*. *J Nat Prod.* 2004; 67(5): 908-910. [CrossRef]
- [24] Pereira RM, Ferreira-Silva GÁ, Pivatto M, Santos LÁ, Bolzani VS, Chagas de Paula DA, Oliveira JC, Viegas C Jr, Ionta M. Alkaloids Derived from Flowers of *Senna spectabilis*, (-)-Cassine and (-)-Spectraline, Have Antiproliferative Activity on HepG2 Cells for Inducing Cell Cycle Arrest in G1/S Transition through ERK Inactivation and Downregulation of Cyclin D1 Expression. *Toxicol in Vitro.* 2016; 31: 86-92. [CrossRef]
- [25] Silva FO, Silva MGV, Cerqueira GS, Sabino EB, Almeida AAC, Costa JP, Freitas RM. Iso-6-Spectraline Effects on Convulsions Induced in Epilepsy Models. *J Young Pharm.* 2011; 3(3): 232-236. [CrossRef]
- [26] Silva FO, Silva MGV, Feng D, Freitas RM. Evaluation of Central Nervous System Effects of Iso-6-Cassine Isolated from *Senna spectabilis* var. *excelsa* (Schrad) in Mice. *Fitoterapia.* 2011; 82(2): 255-259. [CrossRef]
- [27] Viegas C Jr, Bolzani VS, Pimentel LS, Castro NG, Cabral RF, Costa RS, Floyd C, Rocha MS, Young MC, Barreiro EJ, Fraga CA. New Selective Acetylcholinesterase Inhibitors Designed from Natural Piperidine Alkaloids. *Bioorg Med Chem.* 2005; 13(13): 4184-4190. [CrossRef]
- [28] Castro NG, Costa RS, Pimentel LS, Danuello A, Romeiro NC, Viegas C Jr, Barreiro EJ, Fraga CA, Bolzani VS, Rocha MS. CNS-Selective Noncompetitive Cholinesterase Inhibitors Derived from The Natural Piperidine Alkaloid (-)-Spectraline. *Eur J Pharmacol.* 2008; 580(3): 339-349. [CrossRef]
- [29] Ellman GL, Courtney KD, Andres V Jr, Featherstone RM. A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity. *Biochem Pharmacol.* 1961; 7(2): 88-95. [CrossRef]
- [30] Ingkaninan K, Temkitthawon P, Chuenchom K, Yuyaem T, Thongnoi W. Screening for Acetylcholinesterase Inhibitory Activity in Plants Used in Thai Traditional Rejuvenating and Neurotonic Remedies. *J Ethnopharmacol.* 2003; 89(2-3): 261-264. [CrossRef]
- [31] Sirimangkalakitti N, Olatunji OJ, Changwichit K, Saesong T, Chamni S, Chanvorachote P, Ingkaninan K, Plubrukarn A, Suwanborirux K. Bromotyrosine Alkaloids with Acetylcholinesterase Inhibitory Activity from the Thai Sponge *Acanthodendrilla* sp. *Nat Prod Commun.* 2015; 10(11): 1945-1949. [CrossRef]

This is an open access article which is publicly available on our journal's website under Institutional Repository at <http://dspace.marmara.edu.tr>.

# Source details

## Journal of Research in Pharmacy

Formerly known as: Marmara Pharmaceutical Journal

Scopus coverage years: from 2019 to Present

Publisher: Marmara University

E-ISSN: 2630-6344

Subject area: Pharmacology, Toxicology and Pharmaceutics: General Pharmacology, Toxicology and Pharmaceutics

Medicine: Pharmacology (medical)

Source type: Journal

CiteScore 2021

1.3



SJR 2021

0.189



SNIP 2021

0.372



[View all documents >](#)

[Set document alert](#)

[Save to source list](#)

[CiteScore](#)   [CiteScore rank & trend](#)   [Scopus content coverage](#)

### i Improved CiteScore methodology



CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. [Learn more >](#)

CiteScore 2021

$$1.3 = \frac{476 \text{ Citations 2018 - 2021}}{373 \text{ Documents 2018 - 2021}}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022

$$1.2 = \frac{607 \text{ Citations to date}}{487 \text{ Documents to date}}$$

Last updated on 05 March, 2023 • Updated monthly

## CiteScore rank 2021

Category	Rank	Percentile
Pharmacology, Toxicology and Pharmaceutics	#42/74	43rd
General		
Pharmacology, Toxicology and Pharmaceutics		
Medicine		
Pharmacology	#181/255	29th

Counts for 4-year timeframe

1 Journal of Research in Pharmacy 1.3 43% 476 373 49

42/74  
General  
Pharmacology,  
Toxicology and  
Pharmaceutics

No minimum selected

Minimum citations

Minimum documents

Citescore highest quartile

[^ Top of page](#)

Show only titles in top 10 percent

1st quartile

2nd quartile

3rd quartile

4th quartile

[Source type](#) [^](#)

Journals

Book Series

Conference Proceedings

Trade Publications



# Journal of Research in Pharmacy

## COUNTRY

Turkey



Universities and research institutions in Turkey



Media Ranking in Turkey

## SUBJECT AREA AND CATEGORY

Medicine

└ Pharmacology (medical)

Pharmacology, Toxicology and Pharmaceutics

└ Pharmacology, Toxicology and Pharmaceutics (miscellaneous)

## PUBLISHER

Marmara University



Marmara University in Scimago Institutions Rankings

## H-INDEX

# 16

## PUBLICATION TYPE

Journals

## ISSN

26306344

## COVERAGE

2019-2021

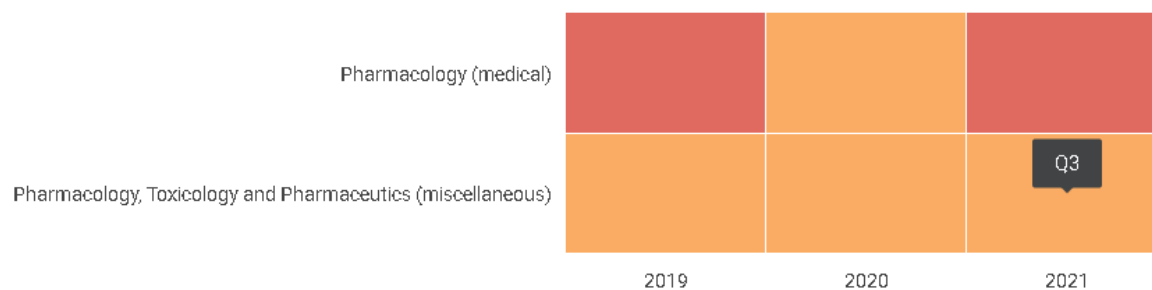
## INFORMATION

[Homepage](#)

[How to publish in this journal](#)

[ikucukguzel@marmara.edu.tr](mailto:ikucukguzel@marmara.edu.tr)

## Quartiles



## SJR



measures the scientific influence of the average article in a journal, it expresses how central to the global scientific discussion an average article of the journal is.

Year	SJR
2019	0.159
2020	0.214
2021	0.189

## Total Documents

