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**Dilnoza ISMATOVA**,  
O'zbekiston Milliy universiteti magistranti  
E-mail: ismatovadilnoz72@gmail.com  
**Sunnatillo SALIMOV**,  
O'zbekiston Milliy universiteti magistranti  
**Orastaxon IBODULLAYEVA**,  
O'zbekiston Milliy universiteti talabasi.  
Tel: +998900187480  
**Asadbek SARABEKOV**,  
O'zbekiston Milliy universiteti katta o'qituvchisi, PhD  
**Salixjan MAULYANOV**,  
O'zbekiston Milliy universiteti dotsenti, k.f.n

O'zbekiston Milliy universiteti professori, k.f.d A.Abdushukurov taqrizi asosida

#### INVESTIGATION AND COMPARATIVE ANALYSIS OF THE BIOLOGICAL ACTIVITY OF KAEMPFEROL AND ITS DERIVATIVES USING IN SILICO MODELS

Annotation

Flavonoids are compounds with high biological activity, exhibiting antioxidant, anti-inflammatory, anticancer, and antimicrobial properties. Kaempferol and its derivatives also clearly demonstrate such activities. This study is dedicated to investigating the biological activity of kaempferol and kaempferol-8-morpholinomethyl. The research was carried out using the GUSAR Online program to predict antibacterial and antifungal activity, while the PASS Online program was employed to forecast various types of biological activity. The results obtained allowed for the identification of the potential pharmacological properties of the compounds and enabled their comparative analysis.

**Keywords:** Kaempferol, morpholine, *In Silico*, GUSAR Online, AntiBac Pred, AntiFun Pred, PASS Online, Pa and Pi values, pharmacological potential.

#### ИЗУЧЕНИЕ И СРАВНИТЕЛЬНЫЙ АНАЛИЗ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ КЕМПФЕРОЛА И ЕГО ПРОИЗВОДНЫХ С ИСПОЛЬЗОВАНИЕМ IN SILICO МОДЕЛЕЙ

Аннотация

Флавоноиды представляют собой соединения с высокой биологической активностью, обладающие антиоксидантными, противовоспалительными, противораковыми и антимикробными свойствами. Кемпферол и его производные также ярко проявляют подобную активность. Настоящее исследование посвящено изучению биологической активности кемпферола и кемпферол-8-морфолинометила. Работа была выполнена с использованием программы GUSAR Online для прогнозирования антибактериальной и противогрибковой активности, а также программы PASS Online для предсказания различных видов биологической активности. Полученные результаты позволили определить потенциальные фармакологические свойства соединений и провести их сравнительный анализ.

**Ключевые слова:** Кемпферол, морфоллин, *In Silico*, GUSAR Online, AntiBac Pred, AntiFun Pred, PASS Online, значения Pa и Pi, фармакологический потенциал.

#### KEMPFEROL VA UNING HOSILALARINING BIOLOGIK FAOLLIKLARINI IN SILICO MODELLARI YORDAMIDA O'RGANISH VA O'ZARO TAQQOSLASH

Annotatsiya

Flavonoidlar yuqori biologik faollikka ega birikmalar bo'lib, ular antioksidantlik, yallig'lanish, rak va mikroblarga qarshi faollik namoyon qilish xususiyatiga ega. Kempferol va uning hosilalari ham bunday faollikni yaqqol namoyon qiladi. Ushbu tadqiqot kempferol va kempferol-8-morfolinometilning biologik faolligini o'rganishga bag'ishlanadi. Tadqiqot GUSAR Online dasturi yordamida bakteriya va zamburug'larga qarshi faolligini, PASS Online dasturi orqali esa biologik faollik turlarini bashorat qilish orqali amalga oshirildi. Olingan natijalar birikmalarning potentsial farmakologik xususiyatlarini aniqlash hamda ularni o'zaro taqqoslash imkonini berdi.

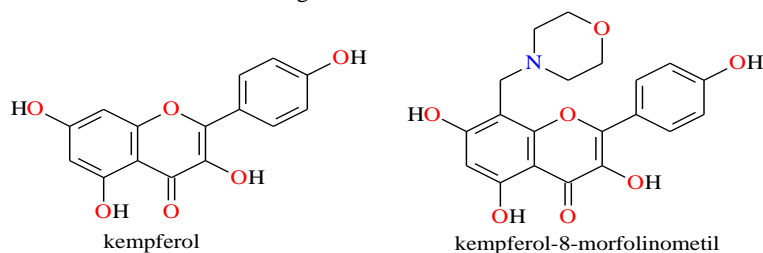
**Kalit so'zlar:** kempferol, morfolin, *In Silico*, Gusar online, AntiBac Pred, AntiFun Pred, Pass online Pa va Pi qiymat, farmakologik potentsial.

**Kirish.** Hozirgi kunda zamonaviy tibbiyotda yangi, samarali, sifatli, xavfsiz, biologik faol birikmalarni yaratish, ularni turli kasalliklarga qarshi muvaffaqiyatli qo'llash yuzasidan dunyo olimlari tomonidan qator ilmiy izlanishlar olib borilmoqda. Biologik faol moddalar orasida flavonoidlar sinfiga mansub birikmalar o'zining faolligi bilan alohida ajralib turadi. Hozirgi kunga qadar flavonoidlarning 4000 dan ortiq turlari qayd qilingan. Jahon sog'liqni saqlash tashkilotining ma'lumotlariga ko'ra flavonoidlar antioksidant va yallig'lanishga qarshi faollikdan tashqari terini himoya qilish, miya funksiyasini yaxshilash, qon shakarini va qon

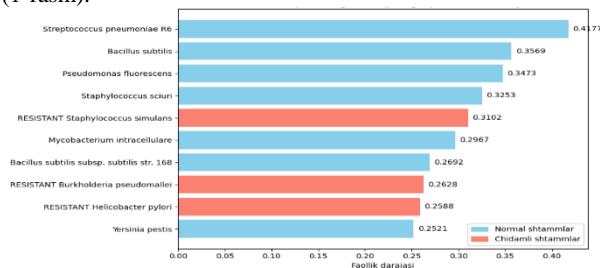
bosimini tartibga solishda ham muhim rol o'ynaydi [1-6]. Kempferol keng qamrovli biologik faollikka ega flavonoid bo'lib, yallig'lanish, antioksidant, infeksiya va saraton hujayralariga qarshi samarali ta'sir ko'rsatadi [7-9]. So'nggi yillardagi tadqiqotlarga asoslanadigan bo'lsak kempferol molekulasining Mannix aminometillash reaksiyasi asosida olingan hosilalarining biologik faolligi kempferolga nisbatan yuqoriligini ko'rish mumkin. Misol uchun T. Kim-Dung Hoang va Shuanglian Cai olimlarning guruhlar tomonidan 6- va 8-C atomiga metilen ko'prigi orqali birikkan amin hosilalari ko'krak saratoni, HeLa, HCC1954 va SK-OV-3 saraton hujayralariga nisbatan o'rtacha va yuqori sitotoksik faollik ko'rsatgan [10-11].

Yangi sintez qilingan moddalarning biologik faolligini *in vitro* va *in vivo* usullarda o'rganish insonda ko'p vaqt va xarajat talab qiladi. *In Silico* usullarida esa yangi sintez qilingan birikmalarning biologik faolligi kompyuter yordamida aniqlanadi, ya'ni modellashtirish yoki simulyatsiya yordamida ilmiy tadqiqotlar olib borilishini anglatadi [12]. Xuddi shunday maqsadlarni amalga oshirish uchun Gusar online va Pass online kabi online dasturlar mavjud. **GUSAR Online** — bu kimyoviy birikmalarning biologik faolligi, toksikligi va farmakokinetik xossalarini *in silico* usulda (ya'ni kompyuter yordamida) oldindan baholashga mo'ljallangan onlayn platforma hisoblanadi. GUSAR — bu "General Unrestricted Structure-Activity Relationships" qisqartmasi bo'lib, umumlashtirilgan QSAR (Structure-Activity Relationship) modellariga asoslangan. Bu dastur **RAS (Rossiya Fanlar Akademiyasi)** tarkibidagi ilmiy guruh tomonidan ishlab chiqilgan. Yangi sintez qilingan birikmalarning bakteriya va zamburug'larga qarshi faolligini o'rganish muhim vazifalardan hisoblanadi. Bu maqsadda Gusar online platformasining AntiBac Pred va AntiFun Pred kabi modullaridan foydalanish mumkin. Ushbu funksiyalar ChEMBL va PASS dasturlarida mavjud bo'lgan bakteriya va zamburug'larga qarshi faollik ma'lumotlaridan foydalangan holda tuzilgan [13]. **PASS Online** (Prediction of Activity Spectra for Substances) - moddaning strukturasi asoslanib 95% gacha biologik faolligini o'rganish imkonini beradi. PASS online dasturida olingan natijalar (biologik faollik turlari) Pa (Possible activity) va Pi (Possible inactivity) son qiymatlari ko'rinishida taqdim qilinadi [14]. Yangi sintez qilingan moddalarning biologik faolliklarini o'rganish orqali ularning farmakologik potensialini baholash mumkin. Tadqiqot davomida kempferol hamda 3,5,7-trigidroksi-2-(4-gidroksifenil)-8-(morfolinometil)-4H-xromen-4-on (keyingi o'rinlarda kempferol-8-morfolinometil deb yuritiladi)ni bakteriya va zamburug'larga qarshi hamda PASS inlineda biologik faolligi o'rganildi.

**Tadqiqot metodologiyasi.** Ushbu tadqiqotda Gusar online dasturida AntiBac Pred va AntiFun Pred modullari orqali ikkita moddaning bakteriya va zamburug'larga qarshi faolligi aniqlandi. Bunda Way2Drug dasturiga kirildi va "Service" bo'limidan "AntiBac Pred" tanlandi, modda strukturasi chizib olindi va "Predict Targets for Drawn Structure" qismini bosib turli bakteriya turlariga moddaning qay darajada faollik ko'rsatish tahlil natijalari chiqarildi. Xuddi shunday zamburug'larga qarshi faollik ham "Service" bo'limidagi "AntiFun Pred" moduli orqali amalga oshirildi. Pass online natijalarini olishda esa Way2Drug dasturida ro'yxatdan o'tildi. So'ngra "GO for prediction" bosib akkauntga kirildi va "Predict new compound" dan "Marvin JS" da modda chizib "Predict" qismi bosilganda, moddaga tegishli biologik faollikka doir ma'lumotlar olindi. Yuqoridagi barcha amallar kempferol va kempferol-8-morfolinometil uchun amalga oshirildi.

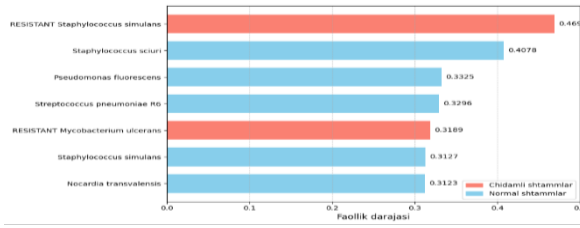


**Tahlil va natijalar.** Dastlab kempferol molekulasini Gusar online dasturidagi AntiBac Pred moduli yordamida bakteriyalarga qarshi faolligi o'rganildi. Olingan natijalarga ko'ra kempferol bakteriyalarning chidamli va normal shtamlariga ham faollik ko'rsatishi aniqlandi (1-rasm).



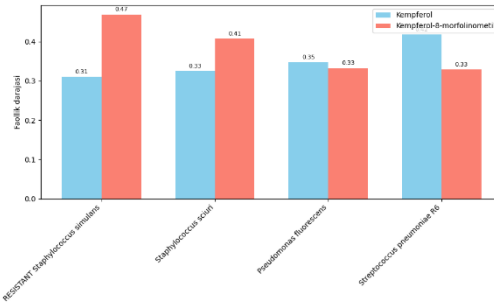
**Rasm 1. Kempferolning bakteriyalarga qarshi faolligi**

Olingan natijalarga ko'ra kempferol birinchi navbatda Streptococcus pneumoniae R6 (0.4177), Bacillus subtilis (0.3569) va Pseudomonas fluorescens (0.3473) kabi bakteriyalarga nisbatan faollikka ega bo'lib chiqdi. Shuningdek, kempferol boshqa bir qator bakteriyalarga, jumladan, Staphylococcus sciuri (0.3253), Mycobacterium intracellulare (0.2967) va Listeria monocytogenes (0.2278) kabi mikroorganizmlarga nisbatan ham sezilarli darajada ta'sir ko'rsatgan. Qiymatlarning 0.3 va 0.4 atrofida bo'lishi juda katta faollikka ega emasligini bildiradi lekin chidamli shtamlarga qarshi ham faollik ko'rsatgani ijobiydir. Tadqiqotning keyingi qismida kempferol-8-morfolinometil hosilasini ham bakteriyalarga qarshi faolligi o'rganildi. Eng yuqori faollik RESISTANT Staphylococcus simulans (0.4693), Staphylococcus sciuri (0.4078) va Pseudomonas fluorescens (0.3325) bakteriyalariga nisbatan qayd etilgan. Bu esa kempferol-8-morfolinometil kempferolga nisbatan bakteriyalarga qarshi faollik xususiyatlari kuchayganini ko'rsatadi (2-rasm).



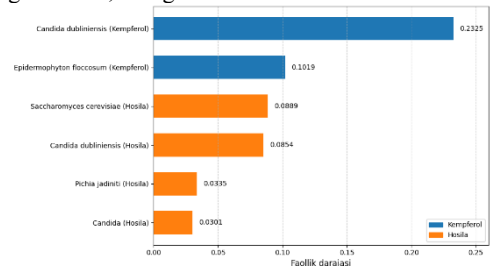
Rasm 2. Kempferol-8-morfolinometilning bakteriyalarga qarshi faolligi

Kempferol va mahsulotning bir tur bakteriyalarga nisbatan faolliklari o'zaro taqqoslandi (3-rasm). Grafik ma'lumotlariga ko'ra kempferol-8-morfolinometilning *RESISTANT Staphylococcus simulans* va *Staphylococcus sciuri* bakteriyalariga nisbatan yuqoriroq faollikka ega bo'lgan. Ayniqsa, chidamli shtamm (*RESISTANT Staphylococcus simulans*) ga nisbatan faollik sezilarli darajada ortgan (0.3102 → 0.4693). Kempferol esa *Streptococcus pneumoniae R6* va *Pseudomonas fluorescens* shtammlariga kempferol-8-morfolinometildan ko'ra faolligi yuqoriroq bo'lgan.



Rasm 3. Turli xil bakteriyalarga qarshi kempferol va kempferol-8-morfolinometilning faolligini taqqoslash

Keyingi bosqichda kempferol va kempferol-8-morfolinometilni zamburug'larga qarshi faolligi o'rganildi. Ikkala modda ham ba'zi tur zamburug'larga qarshi faollik ko'rsatdi, lekin sezilarli darajada faol emas. Kempferol *Candida dubliniensis* ga nisbatan 0.2325 darajada faollik ko'rsatgan bo'lsa, uning hosilasida bu ko'rsatkich 0.0854 ni tashkil etdi.



Rasm 4. Kempferol va kempferol-8-morfolinometilning zamburug'larga qarshi faolligi

Bundan tashqari kempferol va kempferol-8-morfolinometilning Pass online dasturida biologik faolliklari o'rganildi. Bunga ko'ra kempferolda Pa>0.7 bo'lgan 100 ta biologik faollik namoyon bo'ldi, aksincha kempferol-8-morfolinometilda esa Pa>20 ta faollik ko'rsatdi. 1-jadvalda kempferol va 2-jadvalda kempferol-8-morfolinometilning Pa qiymati yuqori bo'lgan ba'zi faolliklari keltirilgan.

1 - Jadval

Kempferolning PASS onlinedagi ba'zi faolliklari

Kempferol	Pa	Pi
Chlordecone reductase inhibitor	0.983	0.001
Membrane integrity agonist	0.974	0.002
HIF1A expression inhibitor	0.969	0.002
2-Dehydropantoate 2-reductase inhibitor	0.965	0.001
Aryl-alcohol dehydrogenase (NADP+) inhibitor	0.961	0.001
Kinase inhibitor	0.959	0.001
P-benzoquinone reductase (NADPH) inhibitor	0.959	0.001
Membrane permeability inhibitor	0.957	0.002
Peroxidase inhibitor	0.956	0.001
Antimutagenic	0.948	0.001

Umuman olganda kempferol Antineoplastic, TP53 expression enhancer, Apoptosis agonist kabi xavfli o'smalarga qarshi, yallig'lanish va antioksidantlik (Antioxidant, NOS2 expression inhibitor, HMOX1 expression enhancer), CYP1A1 inhibitor, CYP1A2 inhibitor, Aldehyde oxidase inhibitor kabi metabolitik jarayonlarda uchraydigan kasalliklarga nisbatan, qon tomir va yurak kasalliklari (Cardioprotectant, Vasoprotector, Hemostatic), gormonal va reproduktiv kasalliklar (AR expression inhibitor, CYP19 inhibitor, Testosterone 17 beta-dehydrogenase inhibitor) larga qarshi yuqori biologik faollik ko'rsatdi. Kempferolning-8-morfolinometilning ba'zi faolliklarini 2-jadvaldan ko'rish mumkin.

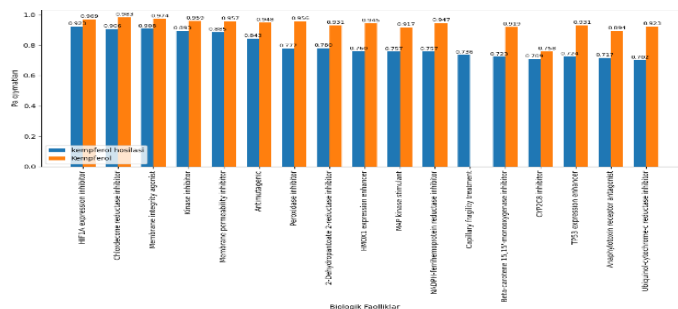
2 - Jadval

Kempferol-8-morfolinometilning PASS onlinedagi ba'zi faolliklari

Kempferol-8-morfolinometil	Pa	Pi
HIF1A expression inhibitor	0.923	0.004
Chlordecone reductase inhibitor	0.906	0.005

Membrane integrity agonist	0.908	0.009
Kinase inhibitor	0.893	0.003
Membrane permeability inhibitor	0.885	0.004
Antimutagenic	0.843	0.003
Peroxidase inhibitor	0.777	0.005
2-Dehydropantoate 2-reductase inhibitor	0.780	0.009
HMOX1 expression enhancer	0.760	0.004
MAP kinase stimulant	0.757	0.004

Kempferol-8-morfolinometil o'sma va saraton kasalliklari (HIF1A inhibitor, TP53 faollashtiruvchi, kinaza inhibitori), yurak – qon tomir kasalliklari, yallig'lanishga qarshi va yuqori antioksidantlik (HMOX1 expression enhancer, Peroxidase inhibitor) faolliklariga ega bo'ldi. Keyingi qismda kempferol va kempferol-8-morfolinometilning turli xil biologik faolliklari o'zaro taqqoslandi (5-rasm).



**Rasm 5. Kempferol va kempferol-8-morfolinometilning PASS onlinedagi biologik faolliklarini o'zaro taqqoslash**

Yuqoridagi rasmdan ko'rish mumkinki, kempferol ham uning hosilasi ham  $P_a > 0.7$  katta bo'lgan juda ko'p biologik faolliklarni namoyish etdi. Grafikdagi  $P_a$  qiymatlardan ko'rish mumkinki, kempferol o'zining hosilasiga nisbatan biologik faolligi ancha yuqori, lekin kempferolning hosilasining ham  $P_a$  qiymati 0.7 dan kattaligi kasalliklarga qarshi dori vositasi sifatida tavsiya berish uchun asos bo'ladi.

**Xulosa.** Kempferol va uning 8-C ga metilen ko'prik orqali morfolinning Mannix birikishidan hosil bo'lgan mahsulotlarning Gusar online va Pass online dasturlarida bakteriya va zamburug'larga ham biologik faolliklari o'rganildi. Kempferol va uning hosilasi bakteriya va zamburug'larga qarshi nisbatan kam faollik ko'rsatdi. Kempferol *Streptococcus pneumoniae* R6 (0.4177) va *Bacillus subtilis* (0.3569) faollik ko'rsatdi. Kempferol hosilasi esa chidamli shtamm *Staphylococcus simulans* (0.4693) va *Staphylococcus sciuri* (0.4078) ga nisbatan faollik ko'rsatdi. Lekin bu ikkala moddani bakteriyalar qarshi qo'llash yaxshi samaradorlikka olib kelmasligi mumkin, chunki faollik darajasi 0.7 past. Pass onlineda olingan natijalarga ko'ra kempferol ham uning hosilasi ham yuqori faollikka ega. Kempferolda  $P_a > 0.7$  dan katta 100 ta faollik bo'lsa kempferolning hosilasida  $P_a > 0.7$  dan katta 20 ta faollik ko'rsatdi. Umuman olganda ikkala modda onkologik kasalliklar, yurak qon tomir kasalliklari, nerv tizimi kasalliklari, yallig'lanish kasalliklariga qarshi faol bo'lib, bu natijalar adabiyotlardagi amaliy tajriba natijalari bilan mos kelganligini ko'rish mumkin.

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