Review article:

Challenges and Opportunities in Repurposing of Drugs: Mini Review

Sindhu S[1] and Murugan S[2]

Abstract:
Repurposing of drugs is an emerging area in the field of medicine. Formulation of new drugs for treating a new clinical condition takes time and consumes a lot of investment. Therefore, there is much attention given towards repurposing of old drugs for new therapy. Majority of drugs approved by FDA for a particular treatment has found applications in the treatment of various other clinical conditions too. In other words, it can be said as 'reusing' of a drug. This mini review focused on the use of repurposed drugs for bacterial infections and cancer treatment. Apart from the benefits of repurposing of drugs, there are some challenges needed to be addressed. Therefore, in this review paper the use of repurposed drugs in treatment of communicable (bacterial infections) and non-communicable (cancer) diseases were discussed.
Keywords: Repurposing of drugs; phase V clinical trial; lifestyle drugs

Bangladesh Journal of Medical Science Vol. 19 No. 03 July'20. Page : 365-371
DOI: https://doi.org/10.3329/bjms.v19i3.45851

Introduction

Drug repurposing, is also known as re-profiling, repositioning, reusing and rediscovery of drugs. The main objective of drug re-profiling is to explore the possibility of using approved drugs for treatment of new diseases[1]. The de novo drug discovery and development can take at least 13 years and cost close to 2 billion dollars[2]. Re-profiled drugs can overcome initial cost and time when compared to formulation of new drugs. Moreover, the rates for repurposed compounds that reach the market are 25% from Phase II and 65% from Phase III clinical trials, in comparison to new molecular entities are 10 and 50%, respectively[1]. Drug re-profiling al1ows investigators to bypass toxicity studies and so it appears to be cost and time-effective[3].

According to Sir James Black (1998), "The most fruitful basis for discovery of a new drug is to start with an old drug"[4]. The repurposing of drugs is sustained by two scientific concepts namely: known target with a new medication and known drug with a new target[1]. FDA has approved many repurposed drugs which were currently introduced into the market. Some of the examples include thalidomide by Celgene corp; which was initially prescribed for nausea and insomnia in pregnant women in 1950, but later it was approved by FDA for the treatment of leprosy in 1998 as Thalomid. Likewise, Azidothymidine which was used for treatment of cancer is now repurposed as an HIV therapeutic and vice versa[5]. Similarly, olaparib, an anticancer agent is under trail for 3rd degree burn[6]. Table 1 shows the list of few FDA approved repurposed drugs.

Table 1 : Repurposed drugs for several indications

Drug	Usual usage	Repurposed to treat	References
Metformin	Anti-diabetic	Pancreatic cancer stem cell	7
Tamoxifen	Breast cancer	Anti-bacterial activity	8
Nilotinib	Leukaemia	Parkinson's disease	9
Raloxifene	Breast cancer	Osteoporosis	10
Liraglutide	Anti-diabetic	Liver disease, weight loss	11,12

1. S Sindhu
2. S Murugan
Department of Biotechnology, School of Agriculture and Biosciences, Karunya Institute of Technology and Sciences, Coimbatore- 641 114, India

Correspondence to: S Murugan, Department of Biotechnology, School of Agriculture and Biosciences, Karunya Institute of Technology and Sciences (Deemed to be University) Coimbatore- 641 114, India, E-Mail ID: micromurugans@gmail.com, murugan@karunya.edu

Drug	Usual usage	Repurposed to treat	References
Amantadine	Anti-viral	Parkinson's disease	13
Aspirin	Pain killer	Heart attack	14
Thalidomide	Sedative	Leprosy	15
Zidovudine	HIV/AIDS	Cancer	16
Ibuprofen	Anti-inflammatory	Anti-microbial	17
Cyclosporine	Rheumatoid arthritis and Psoriasis	Transplant rejection	18
Cycloserine	Urinary tract infection	Tuberculosis	18
Hydroxychloroquine	Rheumatoid arthritis	Anti-diabetic	52
Sildenafil	Hypertension and Angina	Erectile dysfunction	54
Miltefosine	Breast cancer	Anti-leishmanial	22

Opportunities of repurposed drugs in bacterial infections

Bacterial infections have become a major threat to the human population as it becomes a leading cause of death. The overuse, misuse and lack of new antibiotics have led to the development of drug resistant bacteria which is a public menace[19]. These bacterial infections with multiple drug resistance may increase the mortality and morbidity in Intensive Care Unit patients[20]. The multidrug resistance of bacteria occurs mainly due to two mechanisms: (i) accumulation of multiple genes on resistance (R) plasmids, with each coding for resistance to a single drug, within a single cell and (ii) by the action of multidrug efflux pumps, each of which can pump out more than one drug type[55]. Examples of few drug resistant microbes include: i) *E. coli* resistant to cephalosporins and fluoroquinolones, ii) *Klebsiella pneumoniae* resistant to cephalosporins and carbapenems, iii) *Staphylococcus aureus* resistant to methicillin, iv) *Streptococcus pneumoniae* resistant to penicillin, v) Non-typhoidal *Salmonella* resistant to fluoroquinolones, vi) *Shigella species* resistant to fluoroquinolones, vii) *Neisseria gonorrhoeae* resistant to cephalosporins, viii) *Mycobacterium tuberculosis* resistant to rifampicin, isoniazid and fluoroquinolones[56].

Currently researchers are working on developing new antibiotics with some criteria like (i) focussing on new targets and processes like bacterial cell-cell communication that upregulates virulence; (ii) usage of alternate antimicrobials like bacteriophages; (iii) designing inhibitors of bacterial resistance, such as blockers of multidrug efflux pumps[21]. In addition to the development of new antibiotics a different approach of "New uses of old drugs" is a booming concept in pharmaceutics. Clinical survey reports suggested that nearly 24 drugs which are already in use are remarketed for new treatment[22]. Some of the FDA approved repurposed drugs for treating bacterial infections were mentioned in Table 2.

Table 2 : Repurposed drugs for bacterial infections

Drug	Initial Use	New Use	References
Chlorpromazine	Dopamine antagonist to treat schizophrenia	Anti-amoebic, anti-bacterial agents	23
Phenothiazine prototype Methdilazine	Skin allergy	Anti-bacterial agents	23
Trifluoperazine Phenothiazine	Dopamine antagonist to treat schizophrenia	Anti-bacterial agents	23
Oxyfedrine hydrochloride	Used in the treatment of cardiovascular disorders like angina pectoris as vasodilators	Anti-bacterial agents	23
Amlodipine	Anti-hypertensive agent's	Anti-bacterial, Anti-leishmanial and Anti-trypanosomial	23
Dicyclomine	Anti-spasmodic agent	Anti-bacterial agents	24
Ebselen	Anti-atherosclerotic, Anti-inflammatory and Anti-oxidative	Anti-microbial activity	32

Drug	Initial Use	New Use	References
Gallium	Used to treat syphilis in rabbits and trypanosomiasis in mice	Anti-bacterial agents	21
Ciclopirox	Anti-fungal	Bacteriostatic and bactericide activity	21
Auranofin	Anti-rheumatic	Anti-bacterial agents	25
Diflunisal	Non-steroidal and anti-inflammatory	Anti-bacterial agents	26
5-Fluorouracil	Anti-cancer drug Treatment of actinic keratosis and Bowen's disease	Anti-bacterial agents	27
Statins	Lower plasma cholesterol levels	Anti-bacterial agents	28
Terfenadine	Anti-histamine	Anti-bacterial agents	29
Zafirlukast	Treatment of asthma	Anti-mycobacterial	30
Edaravone	Treatment of brain ischemia and myocardial ischemia	Anti-bacterial	52
Salicylanilide	Anti-helmintic	Anti-bacterial	54

Opportunities of repurposed drugs in Cancer Treatment

In the recent days, cancer is a major threat for the community. The cause of cancer due to genetic defects accounts only for 5-10%, whereas 90-95% cases were due to environmental factors and lifestyle[31]. Some of the methods of treatment include surgery, chemotherapy and radiation therapy. In addition complementary treatments like molecular therapy, immunotherapy, apoptosis regulation, anti-angiogenesis therapy, differentiation therapy, signal-transduction therapy, targeted radionuclide therapy and nucleic-acid-based therapies. Moreover, tumour resistance to anticancer drugs is a major problem faced now days[50]. The FDA approved drugs for cancer has declined since 1990s. Due to the lack of enough medications the new concept, drug repurposing of FDA approved non-cancer drugs were developed[49]. Apart from new introduction of drugs discovered for treating cancer, only 5% of drugs enter into phase I clinical trials are continuously used for cancer treatment, therefore already existing non-cancer drugs are tested for its anticancer activities[34]. Previous research reports showed that the treatment using a single agent of drug is less effective than combination therapies as the DNA mutations due to cancer is greater. Therefore repurposing of non-cancer drugs which have undergone preclinical and clinical studies may offer effective treatment for cancer patients[35]. Some of the FDA approved drugs for cancer treatment were depicted in Table 3.

Table 3 : Repurposed drugs for cancer treatment

Drug	Initial Use	New Use	References
Metformin	Diabetes	Breast Cancer	36
Mebendazole	Anti-helminthic	Lung Cancer	37
Aspirin	Stroke	Colorectal Cancer	38
Chloroquine	Anti-malarial	Suppress growth of tumour cells	39
Raloxifene	Osteoporosis	Breast Cancer	40
Thalidomide	Nausea	Bone marrow cancer	41
Cimetidine	Gastric or duodenal ulcer	Colorectal cancer	42

However reports of successful drug repurposing for cancer treatment was limited[35]. Therefore, there is a large gap towards repurposing of drugs for treatment of cancer, thereby researchers have plentiful opportunity in exploring the FDA approved non-cancer drugs for treating of cancer.

Challenges with repurposing of drugs

Apart from benefits, repurposing of drugs faces huge challenges due to which there are limitations in the market for repurposed drugs. Repurposing clinical trials cost a huge amount of money, demonstration of safety needs, efficacy establishment, lack of patent protection and commercialization[2]. Despite the advantages like low cost, less time consuming, the financial support for drug repurposing approaches has been lacking, shorter patent duration, and low return on investment[43]. Moreover, FDA offers only a period of three years exclusively for a new use of previously used drug for a new indication, which is very short period of time to regain the invested money and in case a loss for the pharmaceutical industry[44].

Making Medicalization of certain physiological conditions could be a basis for repurposing of drugs e.g. Sildenafil is used for hypertension and was repurposed for erectile dysfunction. This concept has been discussed under lifestyle drugs[45]. According to Ringel, a drug that has already failed because of toxicity issues cannot be used for new indications. He also suggested that by understanding well about the disease targets and mechanisms, it is possible to overcome market imperfections that prevent repurposing. Some companies are trying to develop platform to build disease matrices and molecules to treat those diseases[46].

Moreover, not all repurposed drugs are successful. For example, bevacizumab, the kinase inhibitor which has been repositioned to many cancers, failed to show its efficacy for gastric cancer in phase III trials[47]. Likewise, multi-kinase inhibitor, sunitinib which was approved for treatment of Gastrointestinal Stromal Tumour (GIST'S), renal carcinomas and pancreatic neuroendocrine tumours failed in its clinical trials for treatment of breast cancer, prostate cancer and Non-small Cell Lung Cancer[48]. The other risks of repurposing of drugs may include side effects for new indications, as the drug has been already used for some other purpose. There should be thorough clinical trials prior to the usage for repurposed drugs. There may be some changes in the concentration of dosage to treat a new indication or may be in the root of administration, as though perfect clinical trials must be carried out.

Conclusion

This mini article is written in a point of view to develop knowledge and awareness among the research community about the upcoming trend "Repurposing of drugs" for communicable and non-communicable diseases. Therefore, repurposing of drug is a blessing for people suffering from diseases caused by multiple drug resistant organisms across the globe. Drug reprofiling therefore has its own benefits and consequences which must be thoroughly studied before making it as a practise. Therefore, a clear view on benefits and consequences of drug-reprofiling can be obtained.

Conflict of interest: None

Source of Fund: Nil

Ethical Clearance: Not Applicable

Author's Contribution

Data gathering and idea owner of the study: Sindhu S and Murugan S

Study Design: Murugan S

Data gathering: Sindhu S

Writing and submitting: Sindhu S and Murugan S

Editing and approval of final draft: Murugan S

References:

1. Agrawal P. Advantages and challenges in drug re-profiling. *J. Pharmacovigil* 2015; S2:e002 https://doi.org/ 10.4172/2329-6887.S2-e002.
2. Shineman DW, Alam J, Anderson M, Black SE, Carman AJ, Cummings JL, Dacks PA, Dudley JT, Frail DE, Green A, Lane RF, Lappin D, Simuni T, Stefanacci RG, Sherer T and Fillit HM. Overcoming obstacles to repurposing for neurodegenerative disease. *Ann Clin Transl Neurol*, 2014; **1** (7): 512–518.
3. Blatt J, Farag S, Corey SJ, Sarrimanolis Z, Muratov E, Fourches D, Tropsha A and Janzen WP[4]. Expanding the scope of drug repurposing in pediatrics: The children's pharmacy collaborative. *Drug Discov Today*, 2014; **19** (11):1696-1698.
4. Robert S. Smart drug reprofiling. Biopharma dealmakers, 2017; Available from: www.cresset-group.com [Accessed on 20 August 2017].
5. Sleigh SH and Cheryl BL. Repurposing strategies for therapeutics. *Pharma Med,* 2010; **24** (3): 151-159.
6. Ahmad A, Olah G, Herndon DN and Szabo C. The clinically used PARP inhibitor olaparib improves organ function, suppresses inflammatory responses and accelerates wound healing in a murine model of third-degree burn injury. *Br J Pharmacol*. 2018; 175 (2): 232-245. https//doi.org/10.1111/bph.13735. Epub 2017.
7. Bednar F and Simeone DM. Metformin and cancer stem cells: old drug, new targets. *Cancer Prev Res*, 2012; **5** (3):351-354.
8. El Arbi M, Théolier J, Pigeon P, Jellali K, Trigui F, Top S, Aifa S, Fliss I, Jaouen G and Hammami R. Antibacterial properties and mode of action of new triaryl butene citrate compounds. *European J Med Chem,* 2014; **76**: 408-413.
9. Pagan F, Hebron M, Valadez EH, Toress-Yaghi Y, Huang X, Mills RR, Wilmarth BM, Howard H, Dunn C, Carlson A, Lawler A, Rogers SL, Falconer RA, Ahn J, Li Z and Moussa C. Nilotinib effects in Parkinson's disease and dementia with lewy bodies. *J Parkinsons Dis,* 2016; **6** (3): 503–517.
10. D'Amelio P and Isaia GC. The use of raloxifene in osteoporosis treatment. *Expert Opin Pharmacother* 2013; **14** (7): 949-956.
11. Candeias EM, Sebastião IC, Cardoso SM, Correia SC, Carvalho CI, Plácido AI, Santos MS, Oliveira CR, Moreira PI, Duarte AI. Gut-brain connection: the neuroprotective effects of the anti-diabetic drug liraglutide. *World J Diabetes* 2015; **6** (6): 807-827.
12. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Ortiz, RV, Jensen CB and Wilding JPH. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015; 373 (1): 11. DOI: 10.1056/NEJMoa1411892.
13. Lee HM and Kim Y, Drug Repurposing is a new opportunity for developing drugs against neuropsychiatric disorders. *Schizophr Res Treatment,* 2016; 6378137.
14. Verma U, Sharma R, Gupta P, Kapoor B, Bano G and Sawhney V. New uses for old drugs: novel therapeutic options. *Indian J Pharmacol,* 2005; **37** (5): 279-287.
15. Anna A Repurposing existing drugs for new indications. The Scientist, Available from: 2017; www.the-scientist.com [Accessed on 3 September 2017].
16. Clouser CL, Patterson SE and Mansky LM. Exploiting drug repositioning for discovery of a novel HIV combination therapy. *J Virol,* 2010; **84** (18):9301-9309.
17. Ogundeji AO, Pohl CH and Sebolai OM. The repurposing of Aspirin and Ibuprofen as a candidate anti-cryptococcus drug. *Antimicrob Agents Chemother,* 2016; 60 (8): 4799-4808.
18. Ann MT. Drug repurposing. *Chemical and Engineering News,* 2012; 90 (40):15-25.
19. Lau QY, Tan YYF, Goh VCY, Lee DJQ, Fui NG, Esther HQ, Hill J and Chia CSB. An FDA-drug library screen for compounds with bioactivities against methicillin-resistant *Staphylococcus aureus* (MRSA). *Antibiotics* (Basel), 2015; **4** (4): 424-434.
20. Maviglia R, Nestorini R and Pennisi M. Role of old antibiotics in multidrug resistant bacterial infections. *Curr Drug Targets,* 2009; **10** (9):895-905.
21. Rangel-Vega A, Bernstein LR, Mandujano-Tinoco EA, Gracia-Contreras SJ and Gracia-Contreras R. Drug repurposing as an alternative for the treatment of recalcitrant bacterial infections. *Front Microbiol,* 2015; **6**:282.
22. Allarakhia M. Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases. *Drug Des Devel Ther,* 2013; 7: 753–766.
23. *Palit P, Subhash CM and Nirup BM.* Reuse of old, existing, marketed non-antibiotic drugs as antimicrobial agents: a new emerging therapeutic approach. Microbial pathogens and strategies for combating them: Science, Technology and Education (Méndez-Vilas, Ed.), 2013; **3**:1883-1892.
24. Karak P, Kumar KA, Mazumdar K, Mookerjee M and Dastidar SG. Antibacterial potential of an antispasmodic

drug dicyclomine hydrochloride. *Indian J Med Res,* 2003; **118**: 192-196.

25. Thangamani S, Mohammad H, Abushahba MF, Sobreira TJ, Hedrick VE, Paul LN and Seleem MN. Antibacterial activity and mechanism of action of auranofin against multi-drug resistant bacterial pathogens. *Sci Rep,* 2016; **6**: 22571.
26. Khodaverdian V, Pesho M, Truitt B, Bollinger L, Patel P and Nithianantham S. Discovery of antivirulence agents against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother,* 2013; **57** (8):3645-52.
27. Walz JM, Avelar RL, Longtine KJ, Carter KL, Mermel LA and Heard SO. Anti-infective external coating of central venous catheters: a randomized, noninferiority trial comparing 5-fluorouracil with chlorhexidine/silver sulfadiazine in preventing catheter colonization. *Crit Care Med,* 2010; **38** (11):2095-102.
28. Rosch JW, Boyd AR, Hinojosa E, Pestina T, Hu Y, Persons DA, Orihuela CJ and Tuomanen EI. Statins protect against fulminant pneumococcal infection and cytolysin toxicity in a mouse model of sickle cell disease. *J. Clin. Invest,* 2010; **120** (2):627-635.
29. Perlmutter JI, Forbes LT, Krysan DJ, Ebsworth-Mojica K, Colquhoun JM, Wang JL, Dunman PM and Flaherty DP. Repurposing the antihistamine terfenadine for antimicrobial activity against *Staphylococcus aureus. J. Med. Chem,* 2014; **57** (20):8540-8562.
30. Pinault L, Han JS, Kan CM, Franco J and Ronning DR. Zafirlukast inhibits complexation of Lsr2 with DNA and growth of *Mycobacterium tuberculosis. Antimicrob Agents Chemother,* 2013; **57** (5):2134-2140.
31. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B and Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res,* 2008; **25 (9): 2097–2116.**
32. Thangamani S, Younis W and Seleem MN. Repurposing ebselen for treatment of multidrug-resistant staphylococcal infections. *Sci. Rep,* 2015; **5**:11596.
33. Thangamani S, Younis W and Seleem MN. Repurposing celecoxib as a topical antimicrobial agent. *Front Microbiol,* 2015; **6**:750.
34. Kato S, Moulder SL, Ueno NT, Jennifer JW, Meric-Bernstam F, Razelle K and Janku F. Challenges and perspective of drug repurposing strategies in early phase clinical trials. *Oncoscience,* 2015; **2** (6): 576–580.
35. Bertolini F, Sukhatme VP and Bouche G. Drug repurposing in oncology-patient and health systems opportunities. *Nat Rev Clin Oncol,* 2015; **12** (12):732-742.
36. Camacho L, Dasgupta A and Jiralerspong S. Metformin in breast cancer - an evolving mystery. *Breast Cancer Res,* 2015; **17** (1):88.
37. Pantziarka P, Bouche G, Meheus L, Sukhatme V and Sukhatme VP. Repurposing drugs in oncology (ReDO)-mebendazole as an anti-cancer agent. *E Cancer Medical Science,* 2014; **8**:443.
38. Chan AT, Shuji O and Charles SF. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med,* 2007; **357**:824-825.
39. Kimura T, Takabatake Y, Takahashi A and Isaka Y. Chloroquine in cancer therapy: a double-edged sword of autophagy. *Cancer Res,* 2013; **73** (1): 3-7.
40. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW, Stepan JJ, Powles TJ, Morrow M, Costa A, Silfen SL, Walls EL, Schmitt H, Muchmore DB, Jordan VC and Ste-Marie LG. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treatment,* 2001; **65** (2):125-134.
41. Thomas DA and Kantarjian HM. Current role of thalidomide in cancer treatment. *Current Opinion in Oncology,* 2000; **12** (6):564-573.
42. Pantziarka P, Bouche G, Meheus L, Sukhatme V and Sukhatme VP. Repurposing drugs in oncology (ReDO)—cimetidine as an anti-cancer agent. *E Cancer Medical Science,* 2014; **8** 485.
43. Guangxu J and Stephen TCW. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. *Drug Discovery Today,* 2014; **19** (5): 637-644.
44. Chong CR and Sullivan DR. New uses for old drugs. *Nature,* 2007; 448: 645-646.
45. Rahman SZ, Gupta V, Sukhlecha A and Khunte Y. Lifestyle Drugs: Concept and Impact on Society. *Indian J Pharm Sci.* 2010; 72(4): 409–413. https://doi.org/10.4103/0250-474X.73902.
46. Eftychia L, Spyros N, Deftereos, Aris P, Andreas P and Christos A. Literature analysis for systematic drug repurposing: a case study from Biovista. *Drug Discovery Today: Therapeutic Strategies,* 2011; **8** (3-4): 103-108.
47. Li YY and Jones SJ. Drug repositioning for personalized medicine. *Genome Med,* 2012; **4** (3): 27.
48. Kim S, Ding W, Zhang L, Tian W and Chen S. Clinical response to sunitinib as a multitargeted tyrosine-kinase inhibitor (TKI) in solid cancers: a review of clinical

trials. *Onco Targets Ther,* 2014; 7: 719–728.

49. Sleire L, Forde-Tislevoll HE, Netland IA, Leiss L, Skeie BS and Enger PO. Drug repurposing in cancer. *Pharmacol Res,* 2017: https://doi.org/10.1016/j.phrs.2017.07.013.

50. Ke X and Shen L. Molecular targeted therapy of cancer: the progress and future prospect. *Frontiers in Laboratory Medicine,* 2017; 1(2): 69-75.

51. Jain V and Gupta OP. Repositioning of drugs: hydroxychloroquine. *J Mahatma Gandhi Inst Med Sci,* 2015; **20**:1-2.

52. Antre RV, Oswal RJ, Thorat DB and Shete RB. Edaravone part 2: antibacterial activity of novel substituted azetidinone derivatives of edaravone. *International Journal of Drug Design and Discovery,* 2012; **3** (2):749-752.

53. Coelho ED, Arrais JP and Oliveira JL. Computational discovery of putative leads for drug repositioning through drug-target interaction prediction. *PLoS Comput Biol,* 2016; **12** (11):e1005219.

54. Rajamuthiah R, Fuchs BB, Conery AL, Kim W, Jayamani E, Kwon B, Ausubel FM and Mylonakis E. Repurposing salicylanili anthelmintic drugs to combat drug resistant *Staphylococcus aureus*. *PLoS ONE,* 2015; **10** (4):e0124595. https://doi.org/10.1371/journal.pone.0124595

55. Nikaido H. Multidrug Resistance in Bacteria. *Annual Reviews of Biochemistry,* 2009; **78**: 119–146.

56. Jyoti T, Shrayanee D, Zeeshan F and Saif H. Multidrug resistance: an emerging crisis. *Interdisciplinary Perspectives on Infectious Diseases,* 2014; 7, http://dx.doi.org/10.1155/2014/541340.