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In – Silico Prediction of Biological Activity Spectrum of Some Existing Local Anesthetic Drugs for Their Novel Anti-infective and Anticancer Potential

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ABSTRACT

Cancer and Infectious diseases now a day's are becoming the major public health issue. The mutations in cancer cell and infectious agents are resulting into new variants which either is resistant or not responding to the current treatment. And discovering novel potential drugs for such new variants is time consuming, complex and laborious process that needs huge money and human efforts. Drug repurposing has attracted attention of world's scientist as it is one of the promising fields that may give quick and cost effective solution for the treatment of such diseases that are affecting major population of the world by utilizing modern bioinformatics and computational resources. Various computational models utilized as a large source of information such as Pubchem, DrugBank, Chemspider, ChEMBL and PASS contains physicochemical and biological information on drugs.

The PASS estimates the probable biological activity profiles for compounds under study based on their structural formulae presented in MOL file or SD file format. Prediction is based on the analysis of structure activity-relationships for more than 250,000 biologically active substances including drugs, drug-candidates, leads and toxic compounds. So we may use PASS for the prediction of the biological activity spectrum for existing drugs and based on the particular interest to some kind of activity and novelty of pharmacological action, we may choose which activities have to be tested experimentally.

In present work the PASS studies of some already existing Local Anesthetics drugs like Benzocaine, Biphenamine, Butacaine, Cyclomethylcaine and Lidocaine were carried out on the Way2Drug portal on PASS online software version 2.0. The PASS study results obtained had revealed that amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine, Cyclomethylcaine, Lidocaine and Ambucaine have shown good Pa value ranging from 0,880 to 0,573 for Antibacterial Activity targets, 0,861 to 0,551 for Antifungal Activity targets and 0,867 to 0,593 for Anticancer Activity targets which predicts the higher probability for these drugs to be active as Antibacterial agents, Antifungal agents and Anticancer agents respectively. Amongst all virtually screened Local Anesthetic drugs Benzocaine was found to possess potent Antibacterial, Antifungal and Anticancer Activities which may be subjected for further evaluation..

Keywords: *PASS, Drug Repurposing, Anti-infective, Anticancer*

1. INTRODUCTION

The word 'Cancer' which instills more fear than the death is the major cause of morbidity and mortality worldwide. The disease has become a big threat globally, irrespective of age, social status, physical fitness, gender, etc. It takes a toll on not just one's health, but also emotions, time and money. The disease not only affects an individual's health – both physically and mentally, but also puts a heavy strain on the financial health of his family. More than 40 lakh cancer cases were reported and 22.54 lakh people died of the disease in the country between 2018 and 2020, the government informed that 13,92,179 cancer cases were reported in 2020; 13,58,415 in 2019; and 13,25,232 cases in 2018. Around 7,70,230 people lost their lives due to cancer in 2020; 7,51,517 in 2019; and 7,33,139 people in 2018 reveals that cancer is one of the leading causes of deaths in India, after heart attack. The most disturbing part is that 71% of the deaths occur in the productive 30-69 age group.

Cancer ranks either first or second among the leading causes of death before the age of 70 years across 91 out of the 172 countries worldwide [1]. The GLOBOCAN 2018, reported 18.1 million new cancer cases and 9.6 million deaths globally

[2]. By 2040, the cancer incidence and mortality are expected to rise to 29.5 million and 16.3 million, respectively [2]. New and challenging problems — rapid urbanization, population ageing, inactive and unhealthy lifestyles, indoor and outdoor air pollution, etc., are responsible for the emerging cancer burden across the globe, majorly impacting the middle-to-low socio-economic countries including India [3].

Chemotherapy remains a mainstay treatment modality in cancer management. Drug resistance during cancer treatment frequently originates with the failure of chemotherapy. Drug resistance is a complex phenomenon that frequently develops as a failure to chemotherapy during cancer treatment. Malignant cells increasingly generate resistance to various chemotherapeutic drugs through distinct mechanisms and pathways. More than 200 anticancer drugs including cytotoxic and biologically targeted agents are currently in use having a low success rate of ~5% in the clinical application[3]. Therefore, identification of novel drug targets and development of effective chemotherapeutic agents to overcome drug resistance in cancer remains a major priority.

Infectious diseases continue to remain one of the most pressing health problems in India. India is the highest infectious disease burden country in the world, which is a major barrier to social and economic development. Amongst the major infectious diseases currently viral, fungal and bacterial diseases with multidrug resistant strains are upcoming and have become one of the major health challenge in the country. To name few, dengue, malaria, flues, tuberculosis, Candidiasis, Aspergillosis, Blastomycosis, Coccidioidomycosis, Mucormycosis, herpes simplex, sexually transmitted infections, like HIV, Gonorrhea, Chlamydia, Syphilis etc.

Tuberculosis is accounting for one fifth of the global incidence - an estimated 1.96 million cases annually(1). Approximately 2.9 million people die from tuberculosis each year worldwide; about one fifth of them in India alone(1). Nearly 500,000 die from the disease – more than 1000 per day–one every minute(2). An estimated 100 million workdays are lost due to illness. The society and the country also incur a huge cost due to TB–nearly US$ 3 billion in indirect costs and US$ 300 million in direct costs(2). The situation is more complicated considering that TB disproportionately affects the young population in India. A nation-wide survey among young children show very high figures of ARTI in almost all the regions- highest in north zone (1.9%) followed by west zone (1.8%), east zone (1.3%.) and lowest in the south zone (1.0-1.1%)(3). The results indicate a high rate of transmission of infection due to high load of infectious cases in the community. ARI and Pneumonia every year are responsible for an estimated 3.9 million deaths worldwide. It is estimated that Bangladesh, India, Indonesia and Nepal together account for 40% of the global ARI mortality(4). On an average, children below 5 years of age suffer about 5 episodes of ARI per child per year, thus accounting about 238 million attacks. According to recent WHO/Unicef data, about 20% of all deaths in children under 5 years are due to acute lower respiratory infections (pneumonia, bronchiolitis and bronchitis); 90% of these deaths are due to pneumonia. Studies have shown that up to 19% of children hospitalized with pneumonia die in India(5).

As per the latest HIV estimates report (2019) of the Government, India is estimated to have around 23.49 lakh people living with HIV/AIDS (PLHIV) in 2019. The HIV epidemic has an overall decreasing trend in country with estimated annual New HIV infections declining by 37% between 2010 and 2019. HIV infection in India is mainly caused by engagement in high risk behaviours. The main high-risk behaviours identified for HIV infection in India includes unprotected heterosexual behaviour, unprotected homosexual behaviour, and unsafe injecting drug use behaviour. There are no dedicated hospitals for the treatment of HIV/AIDS patients. However, under the National AIDS Control Programme (NACP) of the Government, as on July 2020, there are 570 Anti-retroviral treatment (ART) Centers and 1264 Link ART Centers.

Global Trends STDs remain a major public health challenge in the United States.5 While substantial progress has been made in preventing, diagnosing, and treating certain STDs in recent years, CDC estimates that 19 million new infections occur each year, almost half of them among young people aged 15 to 24. Chlamydia remains the most commonly reported infectious disease in the United States. It is estimated that there are approximately 2.8 million new cases of chlamydia in the United States each year. Women, especially young women, are hit hardest by Chlamydia and the long-term consequences of untreated disease are much more severe for women. Gonorrhea is the second most commonly reported infectious disease in the United States.5 In the last 8-10 years, a parallel trend has been noted for gonorrhea and HIV infection, reflecting a common mode of transmission, and similar risk groups for both infections. The highest levels of HPV infection have been reported in the United Kingdom (80-120/100000) and Ireland (100/100000) in 2000. Recently, several outbreaks of lymphogranuloma venereum have been noted in several countries, including Europe, the United States and Canada. It is primarily reported in MSM, among whom the majority is HIV positive.

Current Trends in India STDs constitute a major public health problem for both developing and developed countries. The emergence of HIV infection has increased the importance of measures aimed at control of STDs. A proper understanding of the patterns of STDs prevailing in different geographic regions of a country is necessary for proper planning and implementation of STD control strategies.

The *PASS (Prediction of Activity Spectra for Substances)* is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. *PASS* provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Thus, *PASS* can be used to estimate the biological activity

profiles for virtual molecules, prior to their chemical synthesis and biological testing.

The *PASS* estimates the probable biological activity profiles for compounds under study based on their structural formulae presented in SMILES file, INCHKEY file, MOL file or SD file format. General list of predictable biological activities consists of over 4,000 terms including pharmacotherapeutic effects (e.g., antiarrhythmic), biochemical mechanisms (e.g., cyclooxygenase 1 inhibitor), toxicity (e.g., carcinogenic), metabolism (e.g., CYP3A4 inhibition), gene expression regulation (e.g., VEGF expression inhibition), transporter-related activities (e.g., P-glycoprotein substrate). Prediction is based on the analysis of structure activity-relationships for more than 250,000 biologically active substances including drugs, drug-candidates, leads and toxic compounds.

PASS operates with many thousands of substances from the training set, so provides more objective estimate if a compound is active or not for any kind of activity as compared with any researcher.

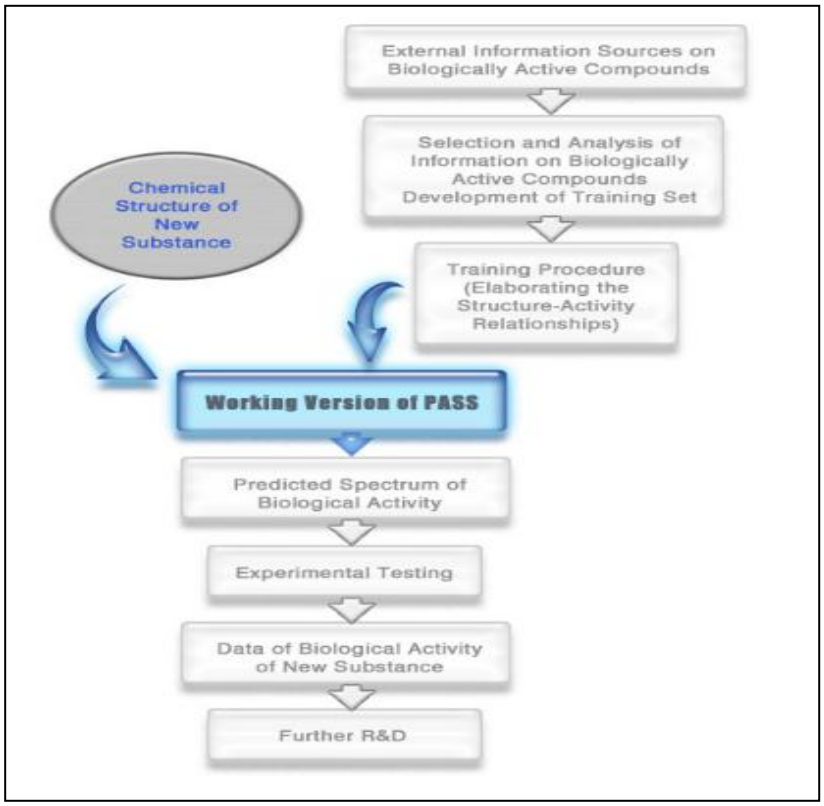


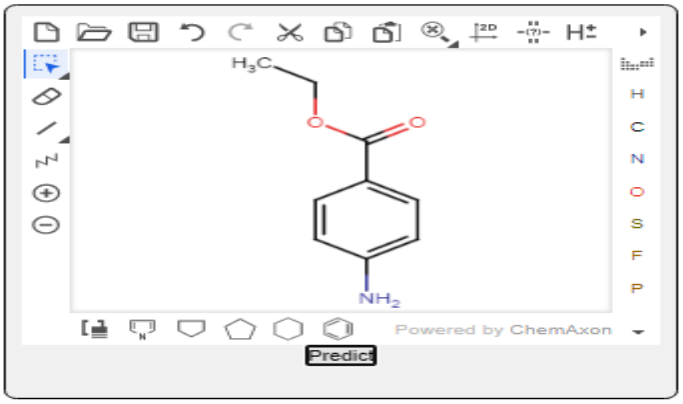
Fig. 01: The process of PASS development and use.

PASS training set covers 6825 kinds of biological activities included basic pharmacological effects, biochemical mechanisms of action, specific toxicities, metabolic terms, influence on gene expression and transporters. Some activities are presented in PASS training set only by one or two compounds; thus such activities are non-included into PASS predictable Activity List.

2. METHODOLOGY:

The activity spectrum of the proposed compound has been predicted by using PASS version 2.0 of Department for Bioinformatics, Institute of Biomedical Chemistry Moscow-119121. This version 2.0 of PASS is developed in (2011). The following protocol is used for the prediction of the activity spectrum of proposed compounds.

To open a new account registration is done on the official website http://www.way2drug.com and after login “Go to PASS prediction” button is clicked. To predict biological activity spectrum of the drug chemical structure of drug under study is required as input file in SDF or MOL formats which are obtained from the chemo informatics and bioinformatics websites like PUBCHEM, OPENBABEL, and CHEMBABEL etc. or from the file converting websites. The chemical structure of drug under study may also be drawn by using Marvin JS. Once the structure is drawn or uploaded then click on the predict button for evaluation of predicted biological activity spectrum of drug under study by PASS software. The results of prediction of spectrum of biological activities are displayed as Pa (“to be active”) and Pi (“to be inactive”) score for the compound under study.



All Pa>Pi Pa>0,3 Pa>0,7 ok

Pa	Pi	Activity
0,908	0,003	Eye irritation, inactive
0,908	0,004	Prolyl aminopeptidase inhibitor
0,905	0,003	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,907	0,006	Methylenetetrahydrofolate reductase (NADPH) inhibitor
0,898	0,003	Arginine 2-monooxygenase inhibitor
0,887	0,003	2-Hydroxymuconate-semialdehyde hydrolase inhibitor
0,887	0,003	3-Hydroxybenzoate 6-monooxygenase inhibitor
0,880	0,002	tRNA-pseudouridine synthase I inhibitor
0,880	0,004	Anesthetic general

Fig. 02: Result of PASS Prediction

3. RESULTS:

The PASS predictions of various local anesthetic drugs for Drug Repurposing approach have been performed and the results obtained are presented below in the table 1.

Table 1: Summary of PASS Study Results of Local Anaesthetic Drugs Exhibiting Potential Antibacterial, Antifungal and Anticancer Activity

Activity	Drug Name	PASS Score		Targets Involved
		Pa	Pi	
Antibacterial				
	Ambucaine			
		0,862	0,004	Membrane integrity antagonist
		0,796	0,010	Membrane permeability inhibitor
	Benzocaine			
		0,880	0,002	tRNA-pseudouridine synthase I inhibitor
		0,852	0,004	UDP-N-acetylglucosamine 4-epimerase inhibitor
		0,851	0,005	Membrane permeability inhibitor
		0,772	0,009	ADP-thymidine kinase inhibitor
		0,658	0,009	Antiinfective-Antibacterial Antifungal
		0,578	0,028	Membrane integrity antagonist
	Biphenamine			

		0,774	0,015	Membrane permeability inhibitor
		0,630	0,027	UDP-N-acetylglucosamine 4-epimerase inhibitor
		0,598	0,023	ADP-thymidine kinase inhibitor
		0,573	0,003	Peptidylamidoglycolate lyase inhibitor
	Butacaine			
		0,756	0,019	Membrane permeability inhibitor
		0,649	0,024	UDP-N-acetylglucosamine 4-epimerase inhibitor
		0,643	0,019	ADP-thymidine kinase inhibitor
	Lidocaine			
		0,699	0,014	ADP-thymidine kinase inhibitor
		0,684	0,019	UDP-N-acetylglucosamine 4-epimerase inhibitor
		0,586	0,004	tRNA nucleotidyltransferase inhibitor
Antifungal				
	Ambucaine			
		0,612	0,021	Superoxide dismutase inhibitor
		0,551	0,068	Sugar-phosphatase inhibitor
	Benzocaine			
		0,861	0,004	N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor – Anticancer – Epigenetic Modifying Enzymes – Antifungal – Sphingamine N-acetyl transferase
		0,841	0,010	Sugar-phosphatase inhibitor
		0,733	0,011	Superoxide dismutase inhibitor
		0,658	0,009	Antiinfective-Antibacterial Antifungal
	Biphenamine			
		0,851	0,004	Membrane integrity antagonist – Antifungal like Azole Class
		0,694	0,012	Prolyl aminopeptidase inhibitor
		0,683	0,037	Sugar-phosphatase inhibitor
		0,640	0,018	Superoxide dismutase inhibitor
		0,576	0 ,060	Phosphatase inhibitor
	Butacaine			
		0,814	0,006	Membrane integrity antagonist
		0,753	0,024	Sugar-phosphatase inhibitor
		0,639	0,018	Superoxide dismutase inhibitor
	Lidocaine			
		0,783	0,008	Superoxide dismutase inhibitor

		0,721	0,011	Prolyl aminopeptidase inhibitor
		0,711	0,013	Membrane integrity antagonist
Anticancer				
	Benzocaine			
		0,867	0,003	Centromere associated protein inhibitor – Anticancer - Ref – 129 – p53 Inhibitor
		0,861	0,004	N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor – Anticancer – Epigenetic Modifying Enzymes – Antifungal – Sphingamine N-acetyl transferase
		0,841	0,010	Sugar-phosphatase inhibitor
		0,685	0,020	Glutathione thiolesterase inhibitor
	Biphenamine			
		0,705	0,018	Glutathione thiolesterase inhibitor
		0,685	0,016	Proteasome ATPase inhibitor
		0,683	0,037	Sugar-phosphatase inhibitor
		0,589	0,010	UGT2B12 substrate
		0,576	0 ,060	Phosphatase inhibitor
	Butacaine			
		0,753	0,024	Sugar-phosphatase inhibitor
		0,593	0,036	Proteasome ATPase inhibitor
	Cyclomethylcaine			
		0,730	0,006	Centromere associated protein inhibitor
		0,468	0,133	Phosphatase inhibitor
	Lidocaine			
		0,782	0,006	Proteasome ATPase inhibitor
		0,763	0,010	Glutathione thiolesterase inhibitor
		0,635	0,047	Sugar-phosphatase inhibitor

4. DISCUSSION:

Biological activity is the result of chemical compound's interaction with biological entity which depends on structure and physico-chemical properties of compounds. Biological activity spectrum of a compound presents every its activity despite of the difference in essential conditions of its experimental determination. Thus, "biological activity spectrum" is defined as the "intrinsic" property of compound depending only on its structure and physico-chemical characteristics.

Any biologically active compound reveals wide spectrum of different effects. Some of them are useful in treatment of definite diseases but the others cause various side and toxic effects. Total complex of activities caused by the compound in biological entities is called the "biological activity spectrum of the substance".

The probability P_a reflects the similarity of molecule under prediction with the structures of molecules, which are the most typical in a sub-set of "actives" in the training set. If, for instance, P_a value equals to 0.9, then for 90% of "actives" from the training set the B values are less than for this compound, and only for 10% of "actives" this value is higher.

Based on these criteria, one may choose which activities have to be tested for the studied compounds on the basis of compromise between the novelty of pharmacological action and the risk to obtain the negative result in experimental testing. Certainly, one will also take into account a particular interest to some kinds of activity, experimental facilities, etc.

In present work the PASS studies of some already existing Analgesic (Non-Narcotic) and Local Aneastheics drugs were carried out on the Way2Drug portal on PASS online software version 2.0. In the above PASS Study Biological Activity Spectrum of some Local Anaesthetic drugs like Benzocaine, Biphenamine, Butacaine, Cyclomethylcaine and Lidocaine was also studied.

The PASS study results portrayed in the above tables revealed that amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine, Lidocaine and Ambucaine have shown good Pa value ranging from 0,880 to 0,573 for Antibacterial Activity targets which predicts the higher probability for these drugs to be active as Antibacterial agents.

The Pa values 0,880 for tRNA-pseudouridine synthase I inhibitor**,** 0,852 for UDP-N-acetylglucosamine 4-epimerase inhibitor**,** 0,851 for Membrane permeability inhibitor**,** 0,772 for ADP-thymidine kinase inhibitor**,** 0,658 for Antiinfective**,** 0,578 for Membrane integrity antagonist predict the targets involved and mechanism of action of **Benzocaine** as potential antibacterial agent. The Pa values 0,774 for Membrane permeability inhibitor**,** 0,630 for UDP-N-acetylglucosamine 4-epimerase inhibitor**,** 0,598 for ADP-thymidine kinase inhibitor**,** 0,573 for Peptidylamidoglycolate lyase inhibitor predict the targets involved and mechanism of action of **Bipheamine** as potential antibacterial agent. The Pa values 0,756 for Membrane permeability inhibitor**,** 0,649 for UDP-N-acetylglucosamine 4-epimerase inhibitor**,** 0,643 for ADP-thymidine kinase inhibitor predict the targets involved and mechanism of action of **Butacaine** as good antibacterial agent. The Pa value 0,699 for ADP-thymidine kinase inhibitor**,** 0,684 for UDP-N-acetylglucosamine 4-epimerase inhibitor**,** 0,586 for tRNA nucleotidyltransferase inhibitor predict the targets involved and mechanism of action of **Lidocaine** as good antibacterial agent. The Pa value 0,862 for Membrane integrity antagonist**,** 0,796 for Membrane permeability inhibitor predict the targets involved and mechanism of action of **Ambucaine** as good antibacterial agent.

The above PASS study results presented in the table revealed that amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine, Lidocaine and Ambucaine have shown good Pa values ranging from 0,861 to 0,551 for Antifungal Activity targets which predict the higher probability for these drugs to be active as Antifungal agents.

The Pa values 0,861 for N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor**,** 0,841 for Sugar-phosphatase inhibitor**,** 0,733 for Superoxide dismutase inhibitor**,** 0,658 for Antiinfective predict the targets involved and mechanism of action of **Benzocaine** as potential antifungal agent. The Pa values 0,851 for Membrane integrity antagonist**,** 0,694 for Prolyl aminopeptidase inhibitor**,** 0,683 for Sugar-phosphatase inhibitor**,** 0,640 for Superoxide dismutase inhibitor**,** 0,576 for Phosphatase inhibitor predict the targets involved and mechanism of action of **Biphenamine** as potential antifungal agent. The Pa value 0,814 for Membrane integrity antagonist**,** 0,753 for Sugar-phosphatase inhibitor**,** 0,639 for Superoxide dismutase inhibitor predict the targets involved and mechanism of action of **Butacaine** as potential antifungal agent. The Pa values 0,783 for Superoxide dismutase inhibitor**,** 0,721 for Prolyl aminopeptidase inhibitor**,** 0,711 for Membrane integrity antagonist predict the targets involved and mechanism of action of **Lidocaine** as good antifungal agent. The Pa values 0,612 for Superoxide dismutase inhibitor**,** 0,551 for Sugar-phosphatase inhibitor predict the targets involved and mechanism of action of **Ambucaine** as good antifungal agent.

The above PASS study results given in the table revealed that amongst virtually screened Local Anaesthetic drugs Benzocaine, Lidocaine, Butacaine, Cyclomethylcaine and Biphenamine have shown good Pa value ranging from 0,867 to 0,593 for Anticancer Activity targets which predicts the higher probability for these drugs to be active as Anticancer agents.

The Pa values 0,867 for Centromere associated protein inhibitor**,** 0,861 for N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor**,** 0,841 for Sugar-phosphatase inhibitor**,** 0,685 for Glutathione thiolesterase inhibitor predict the targets involved and mechanism of action of **Benzocaine** as potential anticancer agent. The Pa values 0,782 for Proteasome ATPase inhibitor**,** 0,763 for Glutathione thiolesterase inhibitor**,** 0,635 for Sugar-phosphatase inhibitor predict the targets involved and mechanism of action of **Lidocaine** as potential anticancer agent. The Pa values 0,753 for Sugar-phosphatase inhibitor**,** 0,593 for Proteasome ATPase inhibitor predict the targets involved and mechanism of action of **Butacaine** as potential anticancer agent. The Pa values 0,730 for Centromere associated protein inhibitor**,** 0,468 for Phosphatase inhibitor predict the targets involved and mechanism of action of **Cyclomethylcaine** as good anticancer agent.

5. CONCLUSION:

In present work the PASS studies of some of the already existing Local Anesthetics drugs Local Anaesthetic drugs like Benzocaine, Biphenamine, Butacaine, Cyclomethylcaine and Lidocaine was studied.

The PASS study results portrayed in the above tables revealed that amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine, Lidocaine and Ambucaine have shown good Pa values ranging from 0,880 to 0,573 for Antibacterial Activity targets which predict the higher probability for these drugs to be active as Antibacterial agents.

Amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine, Lidocaine and Ambucaine have

shown good Pa values ranging from 0,861 to 0,551 for Antifungal Activity targets which predict the higher probability for these drugs to be active as Antifungal agents.

Amongst virtually screened Local Anaesthetic drugs Benzocaine, Lidocaine, Butacaine, Cyclomethylcaine and Biphenamine have shown good Pa values ranging from 0,867 to 0,593 for Anticancer Activity targets which predicts the higher probability for these drugs to be active as Anticancer agents.

Amongst virtually screened Local Anaesthetic drugs Benzocaine, Biphenamine, Butacaine and Lidocaine were found possess all three Antibacterial, Antifungal and Anticancer Activities.

Amongst virtually screened Local Anaesthetics Ambucaine was found possess both Antibacterial and Antifungal Activities.

Amongst virtually screened Local Anaesthetics Cyclomethylcaine showed only Anticancer Activity.

Amongst all virtually screened Local Anaesthetic drugs Benzocaine was found possess potent Antibacterial, Antifungal and Anticancer Activities.

The above PASS studies predicted Membrane integrity antagonist, Membrane permeability inhibitor, tRNA-pseudouridine synthase I inhibitor, UDP-N-acetylglucosamine 4-epimerase inhibitor and 1,4-Lactonase inhibitor as the probable targets involved and mechanisms of action of studied drugs for the Antibacterial Activity.

The above PASS studies predicted Membrane permeability inhibitor, Epigenetic Modifying Enzymes, Sugar-phosphatase inhibitor, Prolyl aminopeptidase inhibitor, Superoxide dismutase inhibitor and Ornithine cyclodeaminase inhibitor as the probable targets involved and mechanism of action of studied drugs for the Antifungal Activity.

The above PASS studies predicted Centromere associated protein inhibitor, N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor, Sugar-phosphatase inhibitor, Glutathione thiolesterase inhibitor, Proteasome ATPase inhibitor, ADP-thymidine kinase inhibitor, Ornithine cyclodeaminase inhibitor, UGT1A substrate and UGT1A3 substrate as the probable targets involved and and mechanism of action of studied drugs for the Anticancer Activity.

Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this research manuscript.

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