REVIEW ARTICLE

Contribution of *Klebseilla Pneumonia* to Antibiotic Resistance of Human Infection: A Review

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ABSTRACT

Advance bacteria have acquired several mechanisms to deal with antibiotics and are becoming more powerful with the passage of time. *Klebsiella pneumoniae* belonging to the class of *Enterobacteriaceae* is also a part of this race and is becoming resistant to almost all types of antibiotics. Colistin which was the last option for treatment is now becoming susceptible to the resistant strains of *Klebsiella pneumoniae*. The modified strain is contributing to human infection via antibiotic resistance and is becoming virulent with the passage of time leading to increase morbidity and mortality rates. On the basis of observations and studies, the first part sum up some important facts associated with the onset of resistance in *Klebsiella pneumoniae* and the symptoms associated with the wild and virulent types. Owing to the ability of antibiotic resistance of *K. pneumonia* cause some infections (UTI and Liver abscesses) in humans are discussed in second part of review.

Keywords: Morbidity, Resistant strain, Susceptible, Antibiotics, Virulents, Infections

INTRODUCTION

The era of 1960s was considered to be the golden era for the development and discovery of new antibiotics. Antibiotics in the previous eras were considered to be the miracle drugs in curing the lethal and pathogenic infections but recently bacteria has acquired resistance to almost each and every antibiotic which has been discovered up to date (Martin, 2004). Development of resistance in bacterial strains is inevitable as with each new antibiotic discovery development of resistance is understood because many of the bacteria carry intrinsic genes responsible for the development of antibiotic resistance in such strains, even if the antibiotics are used appropriately the need to eliminate serious infections lead to the development and selection of sub populations of the bacteria that are resistant to such antibiotics.

Antibiotic resistance is more common in the health care settings especially in the hospitals as well as health care facilities where the patients having serious and lethal infections are treated and are in close proximity to one another such that often they are touched when people in hospitals settings move between them, these factors are responsible for the emergence of resistance and the transmission of resistant strains between and within populations.

Klebsiella pneumoniae is the most crucial bacteria among the emerging antibiotic resistant gram-negative bacterial species causing infections having higher morbidity and mortality rates. First outbreak of infections due to antibiotic resistant *Klebsiella pneumoniae* occurred in northeastern United States. From northern regions of United States the resistant bacteria have been transferred all around the globe. More often routine antibiograms that are generated against the *Klebsiella pneumoniae* give false positive results and then the bacteria that is actually resistant to carbapenems is reported as sensitive. Ertapenem is a type of carbapenem is susceptible to the carbepenemase producing *Klebsiella pneumoniae* and is often an indicator of the presence of carbapenemase resistant *Klebsiella pneumoniae.* The best treatment method to combat these developing resistant infections is yet to be defined however common invitro antibiotic treatment approaches use trigecycline, polymixins and aminoglycosides (Arnold *et. al.,* 2011).

Received on 03-12-2020
Accepted on 18-01-3021

Historical Background: In order to treat infections, antibiotics has been used for more than 70 years and now antibiotic resistance is now being recognized as a worldwide emerging problem in modern medicine (Neill, 2016). The spike of infections caused by Multidrug-Resistant-Drug (MDR) and Extremely-Drug-Resistant (XDR) pathogens affiliated with *Enterobacteriaceae* group. It poses a huge concern since these pathogens are common natural inhabitants of our microbiome (Giske *et. al.,* 2008).

In the present time frame of antibiotic resistance, *Klebsiella pneumoniae* is considered as one of the most concerning pathogens associated with antibiotic resistance. After the German microbiologist Edwin Klebs (1834–1913), the genus was named as *'Klebsiella'* . *Klebsiella pneumoniae* is a gram-negative, non-motile, encapsulated, lactose-fermenting, facultative anaerobic, rod-shaped bacterium. It appears as a mucoid lactose fermenter on MacConkey agar. Several infections are caused by *Klebsiella pneumonia* including liver infection, urinary tract infections, cystitis and pneumonia surgical infections. Furthermore, infections like endocarditis and septicemia are responsible for high mortality rates, prolonged hospitalization and costs (Podschun and Ullmann, 1998).

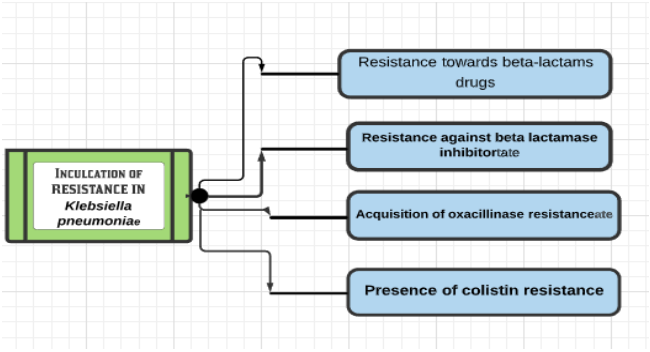
Both humans and animals are its inhabitants and can also exist in water on inanimate objects. It resides on our skin, in nose and throat but commonly it is found in our stool and fecal. The contamination on the hands of caregivers is the prime source of infection among patients (Groopma, 2008). As *Klebsiella* pneumonia is resistant to multiple antibiotics and currently evidence showed that the primary source of the resistance genes is 'Plasmids'. Kelebsiella spp. has the ability to produce extended-spectrum *B*-lactamases (ESBL) are resistant to B-lactam antibiotics excluding carbapenems. Besides this, some

other frequent resistances targets are fluroquinolones, aminoglycosides, tetracycline and chloramphenicol (Nathisuwan *et. al*., 2007).

Here is number of infection cases in this era, such as in Aguust 2016 amid infection of *Klebsiella pneumonia* occurred in a resident of Washoe Country was hospitalized. It was suggested that the microbes get into body while hospitalization and symptoms appeared (Belluz, 2017). Recently, researchers are working to overcome the resistance of *Klebsiella pneumonia* by using multiple efforts for tracking XDR *Klebsiella* using active surveillance for identifying GIT carriage in local. At national level it is reported as highly successful in limiting the insurgence and decreasing the number of new acquisitions (Metan and Akova, 2016).

Emergence of Antibiotic resistance in *Klebsiella pneumonia"* *Klebsiella pneumoniae* is resistant to all commonly used antimicrobial agents. These have been recognized as emerging infectious agents of clinical significance. The emergence of such resistant at global level is challenging for clinicians with rare therapeutic options left for countering these pathogens. Here, given below in the fig. 1 is the flowchart representing some antibiotics which are resistant to *Kelebsiella pneumoni*a, hence, has developed resistance via mutation in the gene strain.

Fig. 1: Emergence of Antibiotic Resistance in *Klebsiella pneumoniae* emergence of resistance towards beta-lactams drugs



Klebsiellela pneumoniae is found to be resistant to antibiotics globally especially to beta lactam antibiotics such as cephalosporins and carbapenams. The SHV-2 gene in *Klebsiella pneumoniae* is associated with the production of extended spectrum beta lactamases that ultimately attack the beta lactam drugs and hence the bacteria can easily persist inside the human body (MacKenzie *et. al*., 1997).

Emergence of resistance against beta lactamase inhibitor: Resistance to carbapenems is now becoming an important concern worldwide. Carbapenemase producing strains of *Klebsiella pneumoniae* are associated with the higher mortality rates in infected individuals. Even this issue is getting even complicated because of the fact that the bacteria are becoming resistant to beta lactamase inhibitors as well and this is an alarming situation in the field of medicine and pharmacology. The most important example in this scenario is the presence of resistance against ceftazidime-avibactam which was being used as a novel beta lactamse inhibitor in order to combat beta lactamase resistance, this was found to be associated with *Klebsiella pneumoniae* carbapenemase type 3 which was being produced by a gene $bla_{KPC-3.}$ Whole genome sequencing revealed that this gene is actually a result of a mutation event and thus is now getting itself globalized all around (Shields *et. al*., 2017).

Acquisition of oxacillinase resistance in *Klebsiella pneumonia:* In 2001, a strain of *Klebsiella pneumoniae* isolated in Turkey was found to be resistant against all different types of beta-lactam drugs including the cabapenems. When the genome was sequenced for identification of the genes associated with the production of these lactamases and the genes that were isolated were cloned and expressed in Escherichia coli and the results indicated that there are 5 different types of beta-lactamses being produced in *Klebsiella pneumoniae*. Out of these 5 lactamases the most important was 0XA-48 because of its higher hydrolyzing power and it can easily hyudrolyze imipenem at a sufficient higher rate comparative to other lactamses, however it lacks the ability to hydrolyze extended spectrum cephalosporins. The gene that was found to be associated with the production of OXA-48 was present in the plasmid thus proving the fact that most of the antibiotic resistant genes are present on the plasmids. However the other oxacillinase genes were found to be associated with the integrons but this gene is plasmid mediated (Poirel *et. al.,* 2004).

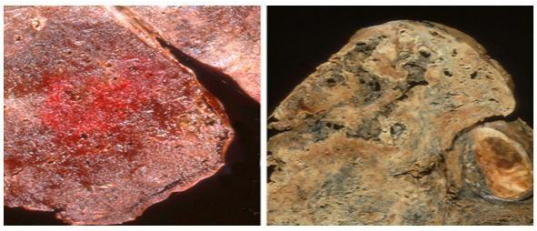
Presence of colistin resistance gene in *Klebsiella pneumonia:* The colistin resistant gene is found to be associated with IncFII-type plasmid and it is named as mcr-8 (plasmid mediated colistin determinant type 8) and is located on 95,983bp which is a transferrable element and the gene is mobile thus increasing the chances of mutations and development of resistance. Acquisition of this gene is therefore strongly related with the onset of resistance to colistin in *Klebsiella pneumoniae.* When BLAST analysis was performed on the gene it was found that the gene has been disseminated into *Klebsiella pneumoniae* causinginfections in humans as well as animals thus increasing the public health burden of resistance to anti-microbials (Wang *et. al*., 2018). Following are some antibiotics mentioned in the tabulation i.e. (Table: 1) which have antibiotic resistance against *Klebsiella pneumonia* when used for the treatment.

Table 1: Antibiotics responsible for Antibiotic Resistance in *Kkebsiella pneumonia*

Antiobiotics	Antibiotic Resistance%	References
Cefixime	82%	Barakzahi *et al.,* 2014
Amoxicillin-clavulanic acid	81.81%	Feizabadi *et al.,* 2007
Cefotaxime	81%	Barakzahi *et al.,* 2014
Aztreonam	78.78%	Feizabadi *et al.,* 2007
Piperacillin	60.6%	Bina *et al.,* 2015
Tazobactam	15.15%	Feizabadi *et al.,* 2007
Carbapenem	14%	Bina *et al.,* 2015
Imipenem	13.9%	Bina *et al.,* 2015
Amikacin	11.9%	Kumar, 2013

Mechanisms of resistance in *Klebsiella pneumonia:* There are various mechanisms by which *Klebsiella pneumoniae* acquire resistance to antibiotics and thus make the diseases more complex and complicated. These mechanisms are represented through tabulation (fig. 2) and discussed as under; (Garbati and Godhair, 2013)

Fig. 2: Mechanism of Resistance in *Klebsielia Pneumoniae*



Presence of mobile genetic elements: One important factor contributing towards antibiotic resistance in *Klebsiella pneumoniae* is the presence of mobile genetic elements in the genome of *K. pneumoniae.* These genetic elements in the genome carry resistant genes and thus can easily be relocated anywhere in the genome thus transferring the resistant genes and causing mutation thus complicated the whole process and contributing towards the production of carbapenemases and oxacillinases (Lee *et al.,* 2016).

Modification in Lipopolysaccharides: Colistin is an important antibiotic that is used for the treatment of infections caused by gram negative bacilli, however the situation is now been worsened due to the modification in the lipopolysaccharides that are a key component of cell wall of gram negative bacteria. So *Klebsiella pneumoniae* after modifying its lipopolysaccharides can easily attack the colistin thus becoming resistant to colistin and increasing the threat in the antimicrobial World. Another important factor contributing towards colistin resistance is the acquidition of mcr-1 gene (Lee *et al*., 2017).

Capsular protection: Capsule is an important part of gram negative bacteria that increases virulence in the patients. Research has made clear that the capsular proteins can easily me manipulated and thus contributing towards virulence (Doorduijn *et al.,* 2016).

Loss of porins in the outer membrane: As it is understood all gram negative bacterial species have specific proteins in their outer membrane that are referred as porins. Sometimes a mutation event can cause the porins to lose thus making a wild type mutant. It was studied that a mutation event that causes the loss of OMPK35/36 porin combined with the production of extended spectrum beta lactamases confer carbapenem resistance in *Klebsiella pneumonia* (Tsai *et al.,* 2013).

Outer membrane modification in Klebsiella pneumonia: This strategy is adopted in order to combat with most of the polymixins. *Klebsiella pneumoniae* alter its lipopolysaccharides in such a way that the phosphate groups are replaced with 4-amino-4-deoxy-L-arabinose that results in the decrease in negative charge of polysaccharides thus decreasing their ability to bind with polymixins. Sometimes substitution of phosphoethanolamine in the outer membrane reduces the negative charge and hence polymixins cannot bind and eventually become susceptible to the bacteria (Boszczowski *et al.,* 2019).

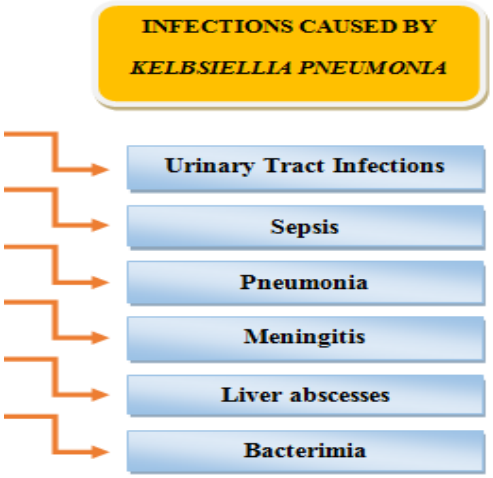
Role of efflux pumps: Efflux pupms play a key role in antibiotic resistance as they selectively allow some material to pass through the membranes. Various chemical and genetic factors are related to the activation of these efflux mechanisms in *Klebsiella pneumoniae* (Pages *et al.,* 2009).

Role of AcrRAB operon: The presence of AcrRAB operon in the genome of *Klebsiella pneumoniae* is responsible to develop resistance against most of the quinolones and antibiotics. It was demonstrated that the strains deficient of this operon are more susceptible to quinolones as well as other antimicrobials comparative to the strains in which the gene was present (Padilla *et al.,* 2010).

In Turkey a study was conducted that prove that efflux pump play a key role in acquiring resistance to antibiotics. A multidrug strain of *Klebsiella pneumoniae* was selected and subjected to an efflux pump inhibitor named as phenylalanine arginine β-naphthylamide (PAβN) acting as an inhibitory substrate for AcrAB/TOLC efflux pump machinery. It was made clear that when the MDR strain was subjected to the efflux pump inhibitor it showed more susceptibility to drugs such as quinolones, tetracycline, and chloramphenicol and beta lactams comparative to the non-treated MDR strain (Hasdemir *et al.,* 2004). The below tabulation form (Table: 2) represents which efflux pump is of *Klebsiella pneumonia* is responsible for antibiotic resistance.

Infections: Infections caused by resistant strains of *Klebsiella pneumoniae* are of greater concern and are more lethal than those caused by its wild strains and hence lead to higher mortality rates, increases healthcare expenditures and prolonged hospitalizations. According to an estimate 47% increased resistance has been observed towards 3rd generation cephalosporins. As the organism is opportunistic pathogen so the rate of infection is comparatively higher in hospital settings comparative to outdoor. There are number of infections caused by *Kelbsiellia pneumonia* in worldwide. Given below in (fig. 3) is the systematic representation of infections caused by *Klebsiella pneumonia.*

Fig. 3: Systematic representation of infections caused by *K. pneumonia*



Sometimes the disease become so complicated that mechanical ventilation needs to be given to patients suffering from infections caused by resistant pathogens. The risk factors that are associated with the onset of infection include solid organ or stem cell transplantation (Patel et al., 2008).

Symptoms associated with the disease: Common symptoms that are associated with *Klebsiella pneumoniae* infection includes:

- Pneumonia
- Urinary tract infections

The infection may occur simultaneously in patients with compromised immune system which may be the result of diabetes mellitus (Podschun and Ullmann, 1998). However with the passage of time the strain has acquired resistance and has become more virulent comparative to the wild strain and has increased morbidity and mortality rates. A strain of *Klebsiella pneumoniae* having a K1 type capsule is associated with increased virulence and following symptoms are observed.

Intraocular spread of infection through blood from liver abscess & spread of infection to central nervous system thus further worsening the situation (Fang *et al.,* 2007). There are two types of infections related to *Kelbsiellia pneumonia.*

1. Nosocomial Infections/ Hospital Acquired *Pneumonias* (HAPs).
2. Community Acquired *Pneumonias* (CAPs). (Paczosa and Mecsas, 2016)

The comparison between nosocomial and community acquired infections is represented in the form of tabulation (Table 2).

Table 2: Efflux Pump of *Klebsiella pneumoniae* Associated with Drug Resistance

Bacteria	Increased Resistance	Components	Family of (Efflux Pumps) EPs	Efflux Inhibitors	References
E. coli	Tetracycline	AcrABTol-C	RND (resistanc-nodulation-cell division)	Chlorpromazine	(Schneiders *et al.,* 2003) (Molnar *et al.,* 1997)
M. tuberculosis	Rifampin	KpnE-F	SMR (small multidrug resistance)	Farnesol	(Srinivasan *et al.,* 2013) (Jin et al. 2010)
Str. Pneumoniae	Fluoroquinolones	OqxA-B	RND (resistance nodulation-cell division)	Reserpine	(Rodriguez-Martinez *et al.,* 2013) (Bansal *et al.,* 2009)
Sta. aureus	Norfl-oxaci-n	KmrA	MFS (major facilitator superfamily)	Flavonoide	Ogawa *et al.,* 2000) Musumeci *et al*., 2003)
Sta. aureus	Fluor-oquinolones	AcrA-B TolC	RND (resistance nodulation-cell division)	Verapa-mil, Reserpi-ne	(Padilla *et al.*, 2009) (Cui *et al.*, 2010)

Table 3: Comparative analysis of Hospital Acquired *Pneumonia* and Community Acquired *Pneumonia*

Nosocomial Infections (HAPs)	Community Infections (CAPSs)	Comparative Analysis	References
Infection caused by *pneumonia*, occurring after two days admission to hospitals.	Infections caused by *pneumonia*, occurring in a person by interaction with the community (outside the hospital)	HAPs are more prevalent than CAPs.	(Paczosa & Mecsas, 2016)
e.g. Pneumonia, UTI, bacteremia	Pyogenic liver abscess, UTI, meningitis	More frequency of etiology of HAPs as compare to CAPs (In Africa, Asia, Australia and Europe)	(Patel PK. *et al*. 2014)
The causative agent is around ~8% to 12%	The causative agent is~3 to 5%.	CAPs are more infectious than HAPs.	(Restrepo MI *et al* 2013)

Here we will discuss two of major infections caused by *Klebsiella pneumonia* in detail which are the rare in worldwide.

Urinary Tract Infections: *Klebsiella pneumonia* are found as the most frequent cause of Urinary Tract Infection behind E. coli and which is responsible for the diverse majority of UTIs. Bacterima, the presence of bacteria in blood is the prime source of Urinary Tract Infection. The primary carrier of K. pneumonia into the environment, are human being. UTIs are thought to arise from seeding of *K. pneumonia* from the Gastrointstinal Tract. Most of the time, *Klebsiella pneumonia* resides around ~2 to 6% of hospital acquired UTIs and 4.3 to 7% of community-acquired UTIs (Laupland *et al*., 2007). Following are mentioned some of the symptoms of Urinary tract infection below:

1. Painful urination
2. Dysuria
3. Frequent urination
4. Blood in the urine
5. Hematuria

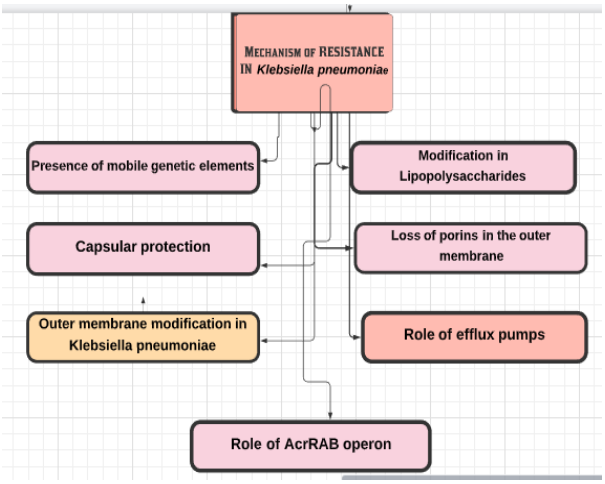
(Jacobsen *et al.,* 2008)

Antibiotics are widely used for the treatment; however some of strains of UTI have acquired resistance against antibiotics, consequences of increasing morbidity rate and long lasting treatment or hospital stay.

Liver Abscesses: It is a group of diseases and is referred to as a syndrome. The common risk factors that might be associated with the syndrome include:

- Compromised immune system
- Patient suffering from diabetes mellitus
- Two distinctive capsular types in *Klebsiella pneumonia*
- After the onset of syndrome the condition further worsen due to the development of metastatic complications such as:
- Meningitis
- Endophthalmitis
- Bacteremia
- Necrotising fasciitis (Siu *et al.,* 2012).

Fig. 4: Liver morphology in Necrotising pneumonia caused by *Klebsiella pneumonia* (Richard and Kradin, 2017).



In the above (Fig. 4) a healthy liver morphology and affected liver morphology is shown, the disease one is slight brown in color affected by *K. pneumonia*. Besides above two major infections, there is a rare infection called 'Meningitis' which is uncommon disease caused by *K. pneumonia.*

Meningitis: Meningitis is a central nervous system infection caused by *Klebsiella pneumoniae* (Friedländer's bacillus), was first detected in 1882 by Friedlabder and first case appeared in 1943 (Thompson *et al.,* 1952). About 30% adults are infected by meningitis and mostly are community acquired infections (Spivack *et al.,* 1957). *Klebsiella pneumonia,* bacterial strain gets into body and cause several infections and meningitis is the rare one. *K. pneumoniae* can cause bacterial meningitis, or inflammation of the membranes that surrounds the brain and spinal cord. In the subarachnoid space, bacteria enter and stimulates the release of pro-inflammatory cytokines and chemokines, boost a host immune response It occurred when bacteria infect the fluid (CSF) around the brain and spinal cord. Most cases of *K. pneumoniae* meningitis happen in hospital settings (Barichello *et al.,* 2013).

Following are some of the symptoms of meningitis, fever, confusion, neck stiffness, sensitivity to bright lights, sleeping, seizures and vomiting

Possible Solutions: Generally in order to prevent spreading of *K. pneumonia* infection, strick precautions must be followed by patients, health care personnel, to avoid dreadful effects. Make habit of washing hands and following Standard Operating Procedures (SOPs) like wearing of gowns and gloves when interacting with patients of *Klebsiella*. The facility that is taking care should prevent the spread of *Klebsiella*. Below are some points given which one should follow to make habit of regular hand washing in order to limit the spread of *Klebsiella* (Tahiry *et al.,* 2010).

- Wash your hands before preparing or eating food.
- Clean your hands before touching eyes, nose and mouth (The T-regions of face).
- After leaving restroom or washroom.
- After dealing with infected wounds (alcohol).
- After sneezing and coughing.
- When you visit hospital make sure to wash hands after touching hospital surfaces

To deal with Multi-Drug-Resistance (MDR) of *Klebsiella pneumpniae* in-vivo technique has been used by intraperitoneal, intravenous and intranasal administration of phages in lab tests (Bogovazova *et al.,* 1991). Healthy people can harbor *Klebsiella* to no detrimental effect as compare to immune-compromised person. Resistance to phages is not likely to be as troublesome as to antibiotics as new infectious phages are likely to be available in environmental reservoirs. Phage therapy can be used in conjunction with antibiotics, to supplement their activity instead of replacing it altogether (Chanishvili, 2012).

CONCLUSION

Klebsiella pneumonia is an important gram negative *bascillus* associated with nosocomial infection and affects only those individuals who have immune-compromised system. With the passage of time the bacteria have adapt itself to its environment and has acquired resistance to antibiotics thus further worsening the situation leading to prolonged infection, increased hospitalization and increased health care expenditures. Thus there is a need for the synthesis of novel antimicrobials to treat such a virulent strain of *Klebsiella pneumoniae* which I think is the only way to combat resistance.

Acknowledgement: The authors would like to acknowledge the Government College, University Lahore for providing this opportunity and supporting this study. Also, the authors would like to thank Dr. Umar Gohar Farooq Assistant Professor and Dr. Hmaid Mukhtar Head of the Department, Institute of Industrial Biotechnology, Government College University Lahore, for reviewing the final version of this manuscript.

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