Original Research Article

Multidrug Resistance in *Klebsiella species* Isolated from Liquid Herbal Remedies in Port Harcourt, Nigeria

ABSTRACT

Aims: *Klebsiella* are lactose fermenting, encapsulated, non-motile, oxidase-negative, gram negative rods; belonging to the family *Enterobacteriaceae*and the non-taxonomic group, coliforms. Pre-isolated *Klebsiella* isolates numbering 109, recovered from 288 samples ofthirty six different liquid herbal medicines to ascertain the prevalence of multidrug resistance (MDR) strains.

Study design: The research is an observational, descriptive, prospective and cross-sectional research. The samples of herbal remedies procured from randomly selected outlets within Port Harcourt metropolis in a completely randomized design.

Place and Duration of Study: The study was conducted at the Depertment of Microbiology laboratory of Rivers State University, Port Harcourt the capital and major city of RiversRivers State in South South Nigeria.

Methodology: The antimicrobial resistance (AMR) patterns of *Klebsiella pneumoniae* and *Klebsiella oxytoca* were determined against 15 antimicrobials, namely amoxicillin clavulanate(30ug/ul), ceftriaxone (30ug/ul), cefuroxime (30ug/ul), cephalexin (30ug/ul), chloramphenicol (30ug/ul), ciprofloxacin (5 ug/ul), cotrimoxazole (25ug/ul), doxycycline (30ug/ul), erythromycin (15 ug/ul), gentamycin (10 ug/ul), levofloxacin (5 ug/ul)norfloxacin (10 ug/ul), ofloxacin (5 ug/ul), peflacine (5 ug/ul), streptomycin (10 ug/ul); by seeding in Muellar-Hinton agar and incubating for 18 to 24 hours.

Results: The cumulative resistance profile for all strainswas45.4%. Doxycycline was the least effective antimicrobial, being resisted by63.3% of the strains, followed by cotrimoxazole (61.5%), erythromycin (58.7%), chloramphenicol (57.8%) and norfloxacin (50.0%). Overall, 82.6% of the *Klebsiella* strains were MDR, extensively drug resistant-XDR, (52.3%) pandrug resistance-PDR (1.8%)and non-multidrug resistant-NMDR (16.0%). *Klebsiella pneumoniae*had MDR (81.6%), XDR (48.8%), PDR(2.0%) and NMDR(18.4%). The MDR strains constituted 90.9% of the *Klebsiella oxytoca* strains all the MDR strains were XDR.

Conclusion: This study has shown that consumption of liquid herbal medicines may result in infection with multidrug resistant strains of *Klebsiella* species. Policy makers are enjoined to incorporate these findings as part of efforts aimed at prevention and control of the menace of multidrug resistance; by formulating and implementing policies aimed atcurtailing contamination of herbal remedies.

Key Words: *Herbal remedy, Multidrug resistance, Antimicrobial Resistance, Klebsiella pneumonae, Klebsiella oxytoca*

Introduction

Klebsiella are lactose fermenting, encapsulated, non-motile, oxidase-negative, gram negative rods; which belong to the non-taxonomic class of enteric bacteria known as coliforms, encompassing such other genera as *Enterobacter, Citrobacter* and *Escherichia. (*Metz et al 2019; Krahulcová*et al* 2022) Taxonomically *Klebsiella* fall under the large, diverse family of the *Enterobacteriaceae*, while the dominant specie of the genus. *Klebsiella pneumoniae* is categorized under the ESKAPE pathogens notable for hyper-virulence and multidrug resistance; and also associated withsevere infections, high morbidity and mortality. Other ESKAPE pathogens include *Enterococcus* spp., *Staphylococcus aureus Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp (Okwu *et al* 2019; Poerio *et al* 2022; Idris &Nadzir 2023)

As an opportunistic pathogen commonly associated with the biota of the mouth, skin, intestines, and in natural environments such as water and soil (Odari&, Dawadi, 2022), *Klebsiella pneumoniae* is recognized as a leading cause of nosocomial and community acquired infections mainly in immuno-compromised persons. It has been linked with diverse infections such as pneumonia, septicemia, and meningitis; infections ofburns, wound, particularly in surgical wards, respiratory tracts, lower biliary ducts, soft tissues, blood, and liver. (Farhadi et al 2021; Awoke *et al* 2021; Odari&Dawadi 2022; Sharma et al 2023)

K. *pneumoniae* owe its emergence as a pathogen of public health concern to the wide array of diseases linked to its multidrug resistant strains which has been implicated in hospital outbreaks across many countries and has considerably served to constrict the antimicrobial treatment options for a large and increasing numbers of infected persons. This has been attributed to its capacity to produce drug resistance enzymes such as extended spectrum-lactamase (ESBLs), carbapenemase, and ability to form biofilms to enrich its arsenal against various antimicrobial agents. (Awoke et al 2021)

Klebsiella oxytoca is a species complex (KoSC) encompassing about nine species, which includes *Klebsiella grimontii*, *Klebsiella huaxiensis*, *Klebsiella michiganensis*, *K. oxytoca*, *Klebsiella pasteurii*, and *Klebsiella spallanzanii*. There are additional three unnamed novel species. (Yang et al 2022)

The species complex is second only to K pneumoniae among members of the genus known to cause clinical infections. (Stewart et al 2022) It is a human commensal and an opportunistic pathogen which has been found to be ubiquitous in soil and water microbiomes. (Ni et al 2021)

Multi-drug resistance (MDR) defined as acquired non-susceptibility to one or more antimicrobial agents from three or more antimicrobial categories (Bhatia et al. 2021; Idris &, Nadzir 2023)has radically altered the response of many pathogens to treatment with antimicrobial agents as increasing number of organisms are becoming resistant to many agents across different categories of antimicrobials. An important measure in the control of the multidrug resistance menace is to study and have a good grasp of the magnitude and dimensions of the challenge to assist healthcare providers in taking vital decisions in the treatment of infections.

This was conceived to ascertain the prevalence of multidrug resistance among *Klebsiella* species obtained from liquid herbal remedies. This will help in providing information on the roles of microbial environment outside the healthcare settings in contributing to the MDR burden and assist in designing control measures.

Methodology

Study design: The research is an observational, descriptive, prospective and cross-sectional research. The samples of herbal remedies procured from randomly selected outlets within Port Harcourt metropolis in a completely randomized design. This study was carried out at the Department of Microbiology Laboratory, Rivers State University, and Port Harcourt, Nigeria.

Identification and Reconfirmation of Isolates

Pre-isolated *Klebsiella* isolates recovered from eight replications of thirty six different liquid herbal medicines in three categories giving a total of 288 samples of herbal remedies were analyzed. The herbal remedy samples were collected in a randomized manner from practitioners and purveyors of herbal medicine within Port Harcourt metropolis in the South-South of Nigeria.

The isolates which had been preserved in 10% glycerol/water solution were cultured on MacConkey agar and incubated under aerobic conditions at 37^0c for 18 to 24 hours. The large, pink and mucoid colonies characteristic of *Klebsiella* were collected, purified and subjected to to morphological and biochemical characterization and identification following the

procedure laid down in “Benson’s Microbiological Applications Laboratory Manual” (Islam *et al* 2018).

Antimicrobial Susceptibility Testing of *Klebsiella* Isolates

Fresh *Klebsiella*colonies were transferred into sterile test tubes containing 3ml of normal saline; the densities of the resultant mixtures were adjusted to match with 0.5 McFarland standards. The inoculums were seeded on Muller Hinton agar with the following antibiotics: amoxicillin clavulanate(30ug/ul), ceftriaxone (30ug/ul), cefuroxime (30ug/ul), cephalexin (30ug/ul), chloramphenicol (30ug/ul), ciprofloxacin (5 ug/ul), cotrimoxazole (25ug/ul), doxycycline (30ug/ul), erythromycin (15 ug/ul), gentamycin (10 ug/ul), levofloxacin (5 ug/ul)norfloxacin (10 ug/ul), ofloxacin (5 ug/ul), peflacine (5 ug/ul), streptomycin (10 ug/ul). The cultures were incubated for 18 to 24 hours; while zones of inhibition interpreted in accordance with the recommendations of the Clinical Laboratory Standards Institute (CLSI).

Results

The results of the resistance and susceptibility profiles of all the isolates are illustrated in table 1. The cumulative resistance profile for all the 109 strains of *Klebsiella*analyzed against 15 antimicrobial agents belonging to eight different antimicrobial categories was found to be **45.4**%. The tetracycle antibiotic, doxycycline was the overall least effective antimicrobial as it was observed to be ineffective against 63.3% of the strains, followed by the folate pathway inhibitor cotrimoxazole (61.5%) the macrolide erythromycin (58.7%), the phenicol chloramphenicol (57.8%) and the first generation fluoroquinolone, norfloxacin (50.0%).

The non-regulated herbal remedies recorded the highest cumulative resistance profile having **49.5**%, of the *Klebsiella* strains being cumulatively resistant to the all the tested antimicrobials. Doxycycline and Erythromycin with resistant profile of 71.0% apiece recorded the least effect on the isolates, followed by cotrimoxazole (67.7%) and chloramphenicol (64,5%). The home-brewed remedies amassed a cumulative resistance of **45.3**% and had the cotrimoxazole and doxycycline as most resisted agents as each of the was resisted by 65.5% of the strains, followed by erythromycin (55.2). The regulated herbal remedies recorded the least cumulative resistance profile of all the three categories of herbal remedies with a profile of **42.9%).**

The cumulative resistance profile for the *Klebsiella pneumoniae strains* as shown on Table 2, was found to be 45.0%; the least effective antimicrobial agent was doxycycline (62.2%), followed by cotrimoxazole (61.2%) and erythromycin (58.2%). Among the *Klebsiella*

pneumoniae strains obtained from the non-regulated herbal remedies, the cumulative resistance profile was 49.3%; doxycycline logged the highest resistance profile with 75.0%, followed by cotrimoxazole and erythromycin with profiles of 71,4% apiece. The cumulative resistance profile against the *Klebsiella pneumoniae* strains obtained from the home-brewed herbal remedies, was observed as 44.9%; doxycycline had the highest resistance profile of 65.6%, cotrimoxazole recorded 61.5% and erythromycin logged 57.7%. The *Klebsiella pneumoniae* strains found in the regulated herbal remedies recorded a cumulative resistance profile was 57.7%; cotrimoxazole had a profile of 54.5%, chloramphenicol and erythromycin recorded 52.3% each.

The cumulative resistance profile for the *Klebsiella oxytoca strains*was found to be 53.9% and a corresponding susceptibility of 46,1%; the highest resistance profile were observed with chloramphenicol (81.8%), amoxicillin-clavulanate (72.7%), cefuroxime (72.7%) and doxycycline (72.7%). The strain of *Klebsiella oxytoca* recovered from the non-regulated herbal remedies logged a cumulative resistance profile was 62.2% and susceptibility profile of 37.8%; 11 of the 15 antimicrobial agents logged more than 60% resistance against the strains with two of the agents cefuroxime and chloramphenicol, recording 1oo% resistance. The cumulative resistance profile against the *Klebsiella oxytoca strains* obtained from the home-brewed herbal remedies

was observed as 48.9% and a susceptibility profile of 51.1; 8 0f the 15 antimicrobials had resistance profiles of 67.0%. The *Klebsiella oxytoca* strains found in the regulated herbal remedies recorded a cumulative resistance profile was 52.0% (Table 3)

Table1: Antimicrobial Resistance Profiles of *Klebsiella pneumoniae* and *Klebsiella*

Antimicrobials	**Non-Regulated (n=31)**		**Regulated (n=49)**		**Home-brewed (n=29)**		**Total (n=109)**	
	R	**R%**	**R**	**R%**	**R**	**R%**	**R**	**R%**
Amoxicillin-clavulanate	14	45.2	24	49.0	13	44.8	51	46.8
Ceftrioxone	11	35.5	18	36.7	11	37.9	40	36.7
Cefuroxime	15	48.4	22	44.9	14	48.3	51	46.8
Cephalexin	14	45.2	25	51.0	12	41.4	51	46.8
Chloramphenicol	20	64.5	27	55.1	16	55.2	63	57.8
Ciprofloxacin	9	29.0	14	28.6	7	24.1	30	27.5
Cotrimoxazole	21	67.7	27	55.1	19	65.5	67	61.5

Doxycycline	22	71.0	28	57.1	19	65.5	69	63.3
Erythromycin	22	71.0	26	53.1	16	55.2	64	58.7
Gentamicin	12	38.7	16	32.7	11	37.9	39	35.8
Levofloxacin	11	35.5	16	32.7	9	31.0	36	33.0
Norfloxacin	18	58.1	21	42.9	15	51.7	54	50.0
Ofloxacin	13	41.9	16	32.7	12	41.4	41	37.6
Pefloxacin	14	45.2	18	36.7	11	37.9	43	39.4
Streptomycin	14	45.2	17	34.7	12	41.4	43	39.4
Aggregate %	**230**	**49.5**	**315**	**42.9**	**197**	**45.3**	**742**	**45.4**

***Oxytoca* Isolates from Liquid Herbal Remedies**

Table 2: Antimicrobial Resistance Profiles of *Klebsiella pneumoniae* Isolates From Liquid Herbal Remedies

Antimicrobials	**Non-Regulated (n=28)**		**Regulated (n=44)**		**Home-brewed(n=26)**		**Total (n=98)**	
	R	**R%**	**R**	**R%**	**R**	**R%**	**R**	**R%**
Amoxicillin-clavulanate	12	42.9	20	45.5	11	42.3	43	43.9
Ceftrioxone	9	32.1	16	36.4	9	34.6	34	34.7
Cefuroxime	12	42.9	19	43.2	12	46.2	43	43.9
Cephalexin	13	46.4	21	47.7	10	38.5	44	44.9
Chloramphenicol	17	60.7	23	52.3	14	53.8	54	55.1
Ciprofloxacin	8	28.6	13	29.5	7	26.9	28	28.6
Cotrimoxazole	20	71.4	24	54.5	16	61.5	60	61.2
Doxycycline	21	75.0	23	52.3	17	65.6	61	62.2
Erythromycin	20	71.4	22	50.0	15	57.7	57	58.2
Gentamicin	10	35.7	14	31.8	9	34.6	33	33.7
Levofloxacin	9	32.1	15	34.1	8	30.8	32	32.7
Norfloxacin	16	57.1	19	43.2	14	53.8	49	50.0
Ofloxacin	11	39.3	15	34.1	11	42.3	37	37.8
Pefloxacin	12	42.9	16	36.4	10	38.5	38	38.8
Streptomycin	12	42.9	16	36.4	11	42.3	39	39.8
Aggregate %	**207**	**49.3**	**279**	**44.3**	**175**	**44.9**	**661**	**45.0**

Table 3: Antimicrobial Resistance/Susceptibility Profiles of *Klebsiella Oxytoca* Isolates from Liquid Herbal Remedies

Antimicrobials	Non-Regulated (n=3)		Regulated (n=5)		Home brewed (n=3)		Total n=11	
	R	R%	R	R%	R	R%	R	R%
Amoxicillin-Clavulanate	2	67	4	80	2	67	8	72.7
Ceftriaxone	2	67	2	40	2	67	6	54.5
Ceforoxime	3	100	3	60	2	67	8	72.7
Cephalexin	1	33	4	80	2	67	7	63.6
Chloramphenicol	3	100	4	80	2	67	9	81.8
Ciprofloxacin	1	33	1	20	0	0	2	18.2
Cotrimoxazole	1	33	3	60	2	67	6	54.5
Doxycycline	1	33	5	100	2	67	8	72.7
Erythromycin	2	67	4	80	1	33	7	63.6
Gentamicin	2	67	2	40	2	67	6	54.5
Levofloxacin	2	67	1	20	1	33	4	36.4
Norfloxacin	2	67	2	40	1	33	5	45.5
Ofloxacin	2	67	1	20	1	33	4	36.4
Pefloxacin	2	67	2	40	1	33	5	36.4
Streptomycin	2	67	1	20	1	33	4	36.4
Aggregate %	**28**	**62.2**	**39**	**52.0**	**22**	**48.9**	**8**	**53.9**

Multidrug Resistance Profiles of *Klebsiella* Isolates from Liquid Herbal Remedies

The analysis of the Multidrug resistant (MDR) profile as shown in Table 4, followed the overlapping denotation of MDR as acquired non-susceptibility (resistance) to at least one antimicrobial in any three or more antimicrobial categories, thus encompassing the extensively drug resistant (XDR) which denotes non-susceptibility to at least one agent in all excepting two or less antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two antimicrobial categories); which also overlaps with Pandrug resistant (PDR) as nonsusceptibility to all agents in all antimicrobial categories.

Overall, 82.6% of the 109 *Klebsiella* Isolates from Liquid Herbal Remedies were found to be multidrug resistant, 52.3% are extensively drug resistant, 1.8% are Pandrug resistant while 16.0% were non-multidrug resistant. *Klebsiella pneumoniae*had 81.6% of the 98 strains being multidrug resistant, **48.8% were** extensively drug resistant, **2.0%** exhibited Pandrug resistant while non-multidrug resistant logged 18.4%. The multidrug resistant strains constituted **90.9% of the** *Klebsiella oxytoca* strains all the MDR strains were extensively drug resistant strains amounting to complete overlapping. There were zero pandrug resistance and 9.1% non-multidrug resistance.

Multidrug resistant strains accounted for 89.7% of *Klebsiella* species recovered from the home-brewed remedies, 51.7%, were XDR, zero pandrug resistant and **10.3% were non-MDR.** *Klebsiella pneumoniae* strains from home-brewed remedies logged **92.3% MDR, 50.0% XDR,** zero PDR and 7.7% non-MDR. The *Klebsiella oxytoca* strains recorded66.7% MDR, 66.7%) XDR, zero PDR and 33.3% non-MDR**.**

The 49 *Klebsiella* Isolates obtained from Regulated herbal remedies logged **73.5% MDR. 36.7% XDR, 2.0% PDR and 22.4% non-MDR. The** *Klebsiella pneumoniae* strains were made up of 75% MDR strains, **34.1% XDR strains, 2.3 PDR strains and 25% non-MDR strains. The** *Klebsiella oxytoca*strains were 100% MDR and XDR.

The Regulated herbal Remedies yielded 31 *Klebsiella* Isolates comprising90.3% MDR strains**,** 77.4% XDR strains, 3.2% PDR strains. The *Klebsiella pneumoniae* strains included 82.1% MDR strains, 67.9% XDR strains, 3.5% PDR strains and**17.6% non-MDR.** The *Klebsiella oxytoca* strains recorded100% MDR and 100%) XDR, zero PDR and zero non-MDR**.**

Tables 4: Multidrug Resistance Profiles of *Klebsiella* Isolates from Liquid Herbal Remedies

Variables	n	NMDR R<3 (R %)	MDR R≥ 3 (R %)	XDR R≥ 6 (R %)	PDR R15(R %)
Non-Regulated Remedies					
Klebsiella oxytoca	3	0	3 **(100%)**	3 **(100%)**	0
Klebsiella pneumoniae	28	5 **(17.6%)**	23 **(82.1%)**	19 **(67.9%)**	1**(3.5%)**
Total	**31**	**5 (16.1%)**	**28 (90.3%)**	**24 (77.4%)**	**1(3.2%)**
Regulated Remedies					
Klebsiella oxytoca	5	0	5 **(100%)**	5 **(100%)**	0
Klebsiella pneumoniae	44	11 **(25%)**	33 **(75%)**	15 **(34.1%)**	1**(2.3%)**
Total	**49**	**11 (22.4%)**	**36 (73.5%)**	**18 (36.7%)**	**1(2.0%)**
Home brewed Remedies					
Klebsiella oxytoca	3	1 **(33.3%)**	2 (**66.7%)**	2 **(66.7%)**	0
Klebsiella pneumoniae	26	2 **(7.7%)**	24 (**92.3%)**	13 **(50.0%)**	0
Total	**29**	**3 (10.3%)**	**26 (89.7%)**	**15 (51.7%)**	**0**
All Herbal Remedies					
Klebsiella oxytoca	11	1 **(9.1%)**	10 (**90.9%)**	10 **(90.9%)**	0
Klebsiella pneumoniae	98	18 **(18.4%)**	80 (**81.6%)**	47 **(48.8%)**	2**(2.0%)**
Total	**109**	**17 (16.0%)**	**90 (82.6%)**	**57 (52.3%)**	**2(1.8%)**

NMDR: Non multidrug resistance; **MDR:** multidrug resistance; **XDR:** Extensively drug resistance **PDR:**Pandrugresistance; **n:** Number of isolates, **R:**resistance

Discussion

This study was conceptualized as surveillance on liquid oral herbal remedies to ascertain the prevalence of multidrug resistance among *Klebsiella* contaminants obtained from such remedies. The outcome of the study will serve to substantially contribute to the wealth of information required for the formulation of policies targeted at the prevention and control of multidrug resistance in the environment. The findings here are considerably in alignment with previous researches which reported high levels of antimicrobial, multidrug resistance to *Klebsiella* (Farhadi et al 2021; Awoke *et al* 2021; Odari&Dawadi 2022; Sharma et al 2023); and justified the placement of *Klebsiella pneumoniae*in the *ESKAPE* category of highly multidrug resistant and virulent pathogens which had been a major issue of global public health alarm.

The outcomes of previous studies on drug resistance in *Klebsiella* or other bacteria have to a greater or lesser extent been disparate; while some results align closely with what was observed here, others higher or lower than this outcome. The MDR profiles observed in this study were high and gives cause for concern with the overall MDR **82.6%),** XDR **(52.3%)** and PDR (1.8%). The preponderance of MDR strains in an organism classified under the ESKAPE group of bacteria with high propensity for the acquisition of resistance genes is a call to expedite action on efforts aimed at reversing the high and increasing prevalence in MDR in *Klebsiella* strains. This correlates with a study of gram negative bacteria which recorded a total MDR of 88.9% for gram negative isolates and 69.0% for *Klebsiella* obtained from clinical specimens (Olowo-Okere *et al* 2020); but departs from another study where the MDR strains were reported as 23.1%, however the same size of 3 isolates was considerably low. (Walusansa*et al* 2021) The departure could be attributed to the small sample size.

The prevalence of antimicrobial resistance in the *Klebsiella* strains in this study is quite high at 45.5%, 45.0% and 53.9% for the total *Klebsiella* strains, *Klebsiella pneumoniae* and *Klebsiella oxytoca* respectively. While the cumulative resistance profile observed for some of the antimicrobials particularlyfuoroquinolones were to some extent close to those reported on same antimicrobials elsewhere. A study on the prevalence of Multidrug Resistant *Klebsiella* species isolated from clinical samples in Cameroun reported levofloxacin, (48.6%), norfloxacin (6 4.9%), ofloxacin, (73.0%) ciprofloxacin (48.6%); as compared to the corresponding findings here viz: 33.0%, 50.0%, 37.6%, 27.5% respectively. Many other antimicrobials in the same study were much more resisted, namelyAmoxicillin Clavulanate (46.8% /86.5%); the cephalosporins cefuroxime (46.8%/ 83.8%) ceftriaxone (34.7%/78.4%) and the folate pathway inhibitor

Cotrimoxazole (61.5% 91.9%); the aminoglycoside gentamicin (35.8%/ 75.7%) (Mbamyah*et al,* 2021). This may be accounted by a number of factors such as the strains of the *Klebsiella* Species, differences in microbiota, innate or acquired resistance of the organisms prior to contamination of herbal remedies, local environmental variables etc. The results obtained here showed closer association with results obtained in a study on clinical gram negative bacteria dominated by *Klebsiella* Species, and *Escherichia coli* ceftriaxone (46.2%) gentamicin (32.5%), ciprofloxacin (50.5%), and trimethoprim-sulfamethoxazole (55.9%) (Olowo-Okere 2020) and Amoxicillin clavulanic acid (63.3%) Gentamycin (4.7%) Ceftriaxone (25.4%) Tetracycline(8.7%) reported in isolates from herbal remedies (Yesuf *et al* 2016).

A major limitation is the absence of genotypic correlations of the results by molecular identification of the resistance appropriate genes due essentially to resource limitations. It is hoped that future studies will endeavor to incorporate the necessary tools to adequately identify the resistance genes. There appears to be inadequacy of researches on multidrug resistance in the environment, researchers are encouraged to beam their searchlights on all nooks and crevices harbouring microorganisms to generate more information required for the menace of drug resistance.This study has succeeded in establishing that one could get infected by multidrug resistant strains of *Klebsiella* Species by consuming liquid herbal medicines while seeking for reliefs from ailments. Policy makers and public health professionals are enjoined to incorporate the findings as part of efforts aimed at prevention and control of the menace of multidrug resistance.

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