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A COMPREHENSIVE ANALYSIS OF RATIONAL AND IRRATIONAL FIXED DOSE COMBINATIONS OF ANTIBACTERIAL DRUGS AVAILABLE IN THE INDIAN MARKET

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ABSTRACT:
INTRODUCTION: Fixed Dose Combinations (FDCs) are products containing two or more active ingredients used for a particular indication, in a fixed ratio of doses. Today, there is a growing concern about the burgeoning list of irrational Fixed Dose Combinations (FDCs) that have flooded the pharmaceutical market in India. Such irrational use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, increasing ADRs and drug interactions which is a serious concern for the health care system. The present study is designed to fill the lacuna in the research regarding rational and irrational FDCs available in the Indian market.
OBJECTIVES:1) To analyse rational and irrational FDCs of antibacterial drugs 2) To create awareness about the extensive use of irrational FDCs among the prescribers.
METHODOLOGY: Data on FDCs available in the Indian market was collected from the Current Index of Medical Specialities (CIMS) Jan-2022[2] and Drug Today Jan-Apr-2022[3] . Their rationality was analysed based on their pharmacokinetic properties, pharmacodynamic activity, drug interactions and those listed in the WHO Essential List Of Medicines 2021[4] and National List of Essential Medicines (NLEM) 2022[5] .The number of companies producing such combinations were listed. A list of prohibited drugs which are still being circulated was also given.
RESULTS: A total of 86 combinations were listed, among which 42 combinations were rational and 44 combinations were irrational. The most common irrational FDC available is Ofloxacin+ Ornidazole, produced by 130 companies. A total of 15 FDCs were found banned but being manufactured by several companies.
CONCLUSION: Many Irrational FDCs are being supplied in the Indian market by different companies. Awareness about irrational FDCs, generated among prescribers through our study, will help to avoid the unnecessary risk of ADRs, drug resistance and financial burden on the patient. Hence, scrutiny and a strict review of regulatory framework for FDC manufacturing and marketing is needed for the betterment of patient care in the country.

KEYWORDS: FDCs, Companies, Antibiotics, Banned Drugs, Irrational

INTRODUCTION

Fixed Dose Combinations (FDCs) are products containing two or more active ingredients used for a particular indication in a fixed ratio of doses.[1] When two or more drugs are combined in a single formulation, the safety, efficacy and bioavailability profiles of the established drugs change. Hence, FDCs are treated as new drugs.[1]

Today, the use of FDCs has become increasingly high either due to improved compliance or from the added effects of the combined two drugs. Thus, they are used for the treatment of a wide variety of diseases.

But do the prescribed FDCs benefit or also cause harm? In other words ,are these rational or irrational combinations that are given to the patients?

The FDCs are called "rational" when the drugs in the combination act by different mechanisms, the pharmacokinetics of the individual drugs must not be widely different and the combination should not have supra-additive toxicity of the ingredients.[7]

There is a growing concern about the irrational FDCs which have flooded the pharmaceutical market in India. Such irrational use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, harmful drug interactions, increasing Adverse Drug Reactions, financial burden on the patient and other problems. Such problems can give rise to detrimental short-term as well as long-term effects, which is a serious concern for the healthcare system in our resource poor country.

Therefore, the present study aims to fill the lacuna in the research regarding rationality of various antibacterial FDCs in the Indian market. Our study can provide an insight into rational, irrational as well as banned FDCs to the prescribers. This will promote rational use of medicines and ultimately lead to amelioration of patient care in the country.

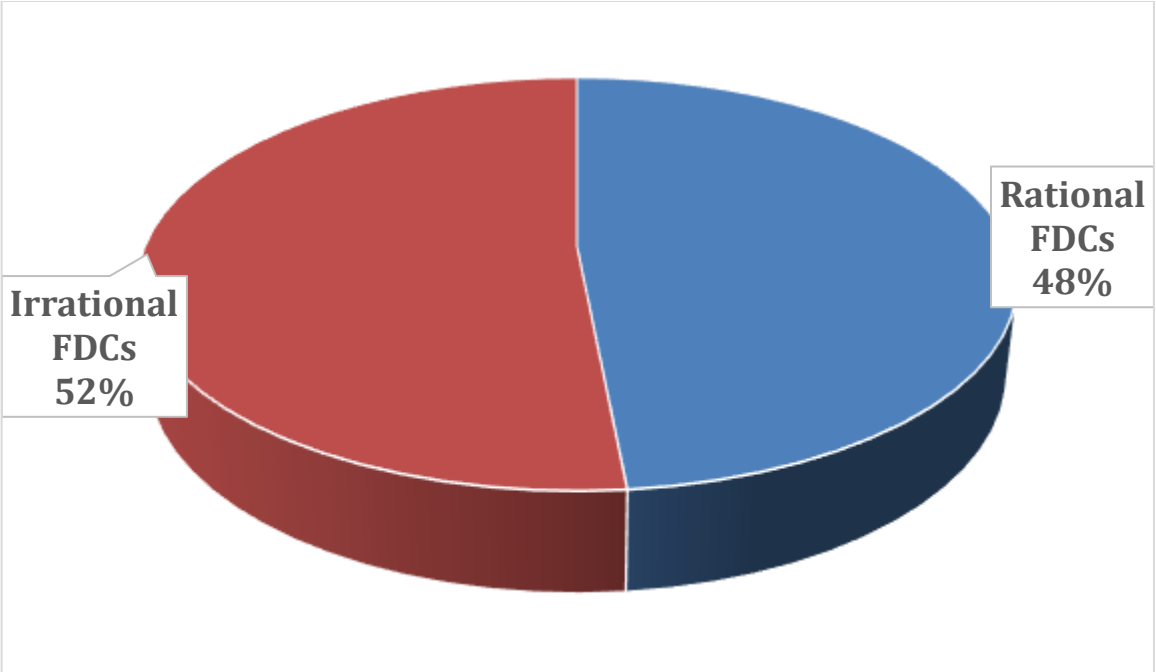
OBJECTIVES

The objectives of the study are to analyse rational and irrational FDCs of antibacterial drug.
and to create awareness about the extensive use of irrational FDCs among the prescribers.

METHODS

The study was conducted at MGM Medical College, Indore. All the antibacterial FDCs available were listed from the given sources: Current Index of Medical Specialities (CIMS) Jan-2022, Drug Today Jan-Apr-2022 and market study . Also, the number of companies producing each FDC was listed. The rationality of each FDC was assessed based on Pharmacodynamic properties, Pharmacokinetic properties, Drug interactions, the WHO Essential List Of Medicines 2021(22nd) list and National List of Essential Medicines (NLEM) 2022.

OBSERVATION AND RESULTS



In our study, a total of 86 Fixed Dose Combinations were listed and their rationality was analysed. Of the total 86 FDCs analysed , 42(48.83%) were found rational and 44(51.16%) were irrational.

The most common rational combination found in our study was 'amoxicillin 500mg + clavulanic acid 125 mg' which was produced by 228 companies .

The most common irrational combination produced by the maximum number of companies was 'ofloxacin 200mg +ornidazole 500 mg' ; by 130 companies.

A total of 44 FDCs were found irrational on the following grounds:-

9 FDCs because of the combination of a Bactericidal drug with a bacteriostatic drug.[7]An example is 'cefuroxime axetil 500mg + linezolid 600mg' produced by 7 companies. Also the FDC 'cefixime 200mg+ azithromycin 500mg' sold by 5 different companies.

Ten FDCs were found irrational due to unnecessary mixed action against different species of Organisms commonly 'Antibacterial plus anti- parasitic combination'[7].For example ofloxacin '400mg + ornidazole 500mg' being sold by 130 companies.

11 combinations were irrational because of 'Action on different spectrum of organisms with no super added effect.'[7] .For eg:- 'ampicillin 250mg + cloxacillin 125mg' were sold by 22 companies. 7 combinations were irrational because of 'Action on different systems'[7].A classic example is 'cefoperazone 500mg/1g + salbutamol 500mg still marketed by 50 companies.

Moreover, banned FDCs are still marketed by a wide variety of companies.15 FDCs are prohibited by CDSCO but sold by a huge number of companies. The FDC 'Ofloxacin 200 mg plus Ornidazole 500mg' is manufactured by 130 companies! Similarly, the suspension of Ofloxacin plus Ornidazole is marketed by 34 companies. The combination of ofloxacin plus metronidazole is circulated by 24 companies and so on.

*The red marked FDCs denote the banned Fixed Drug Combinations banned by the ministry of Health and Family welfare.

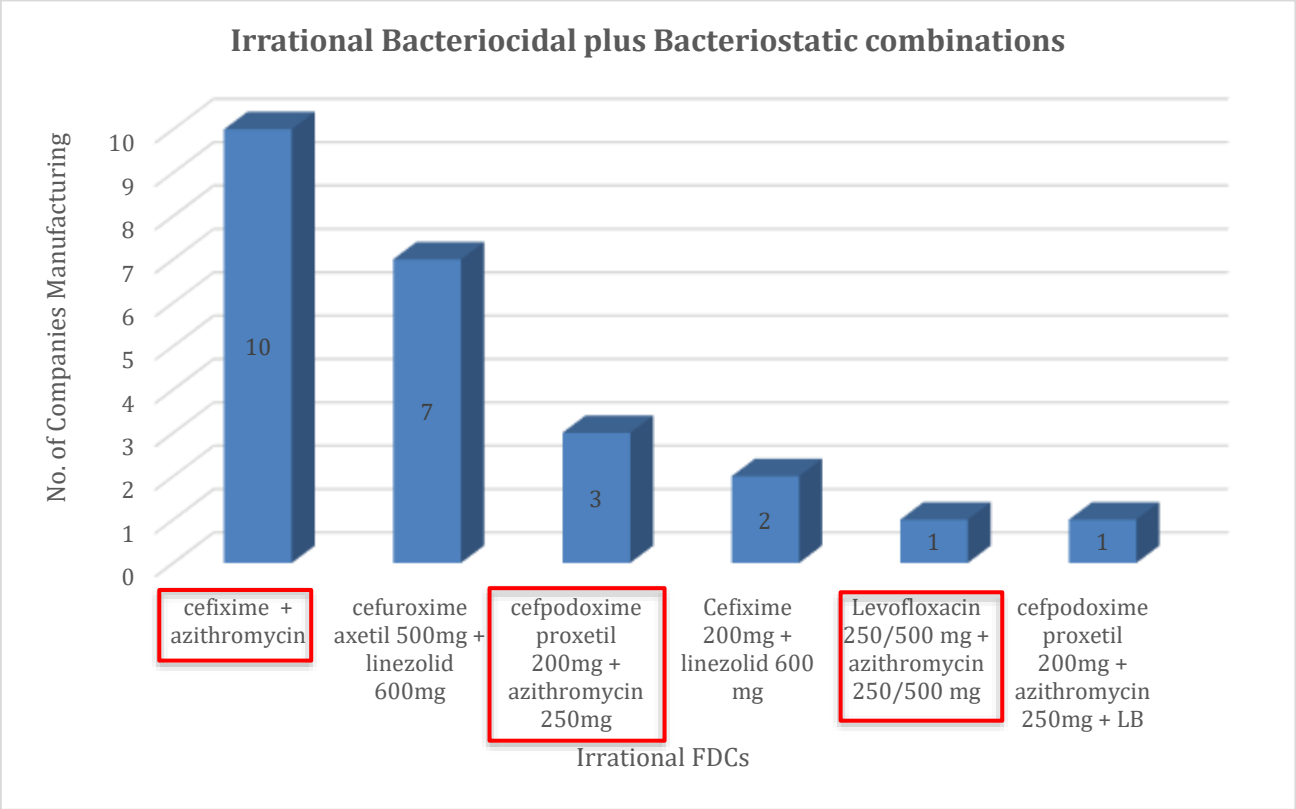


Figure 1 :- Irrationality due to combination of bacteriocidal plus bacteriostatic drugs.

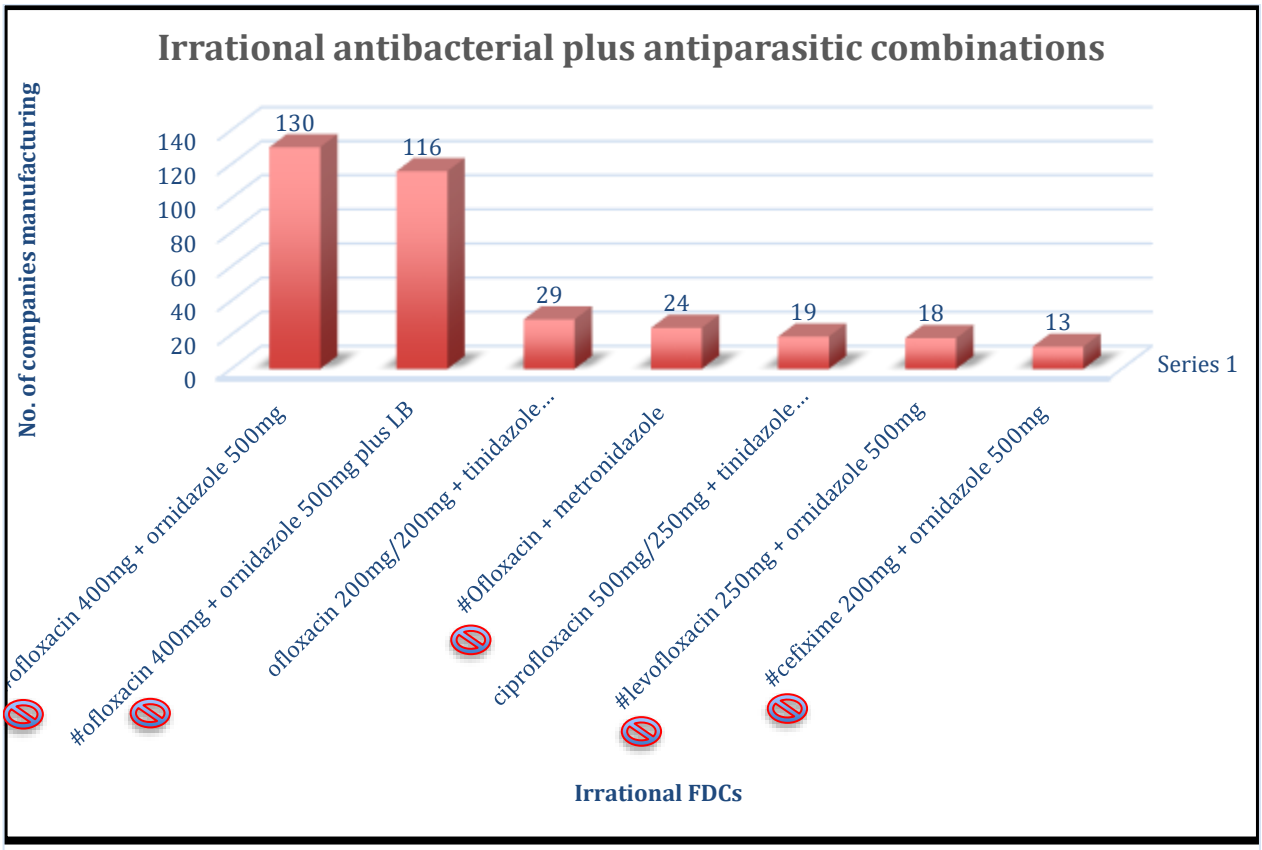


Figure 2 : Irrationality due to the combination of antibacterial plus antiparasitic drugs.

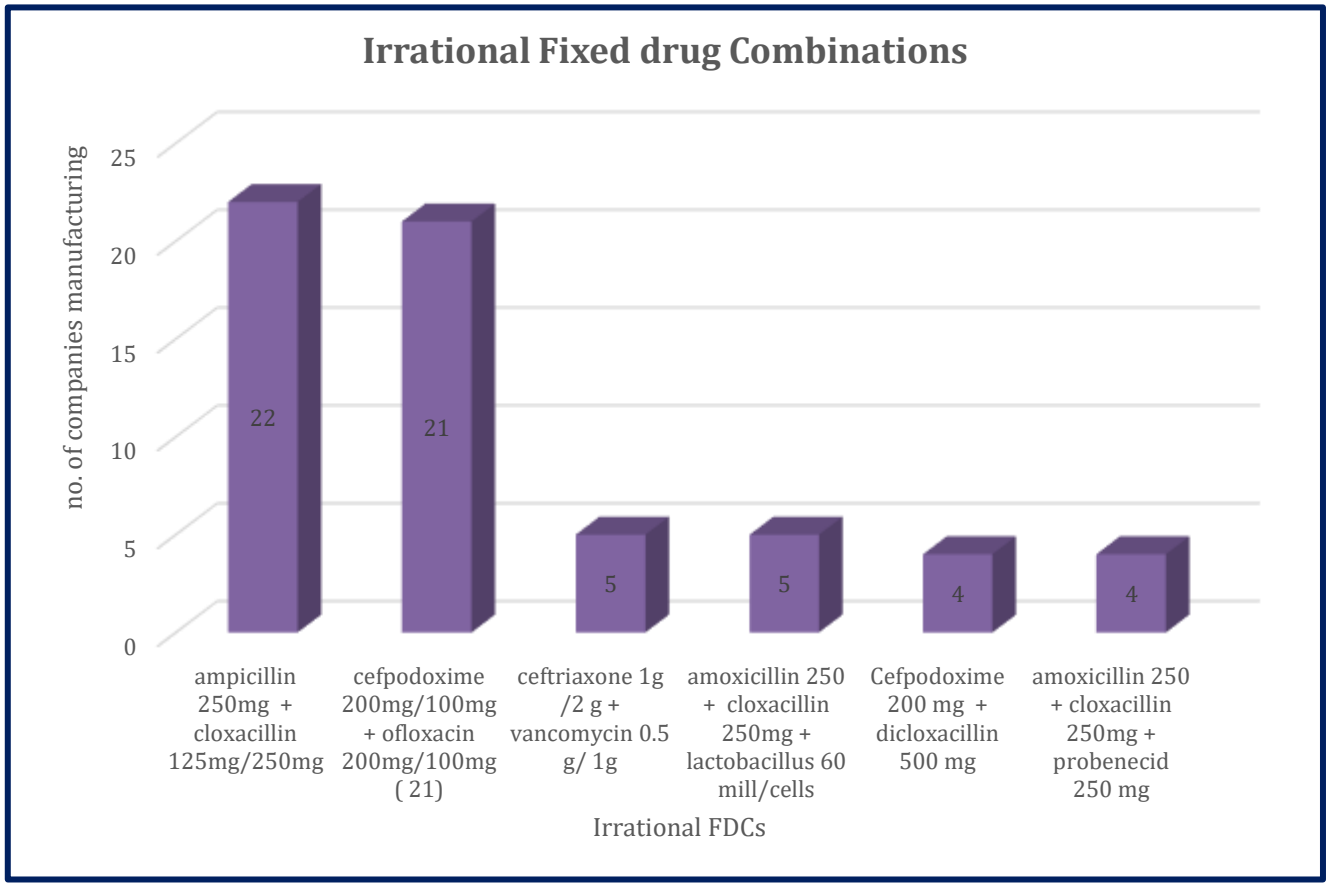


Figure 3 : Irrationality based on action on different spectrum of organisms , no superadded effect

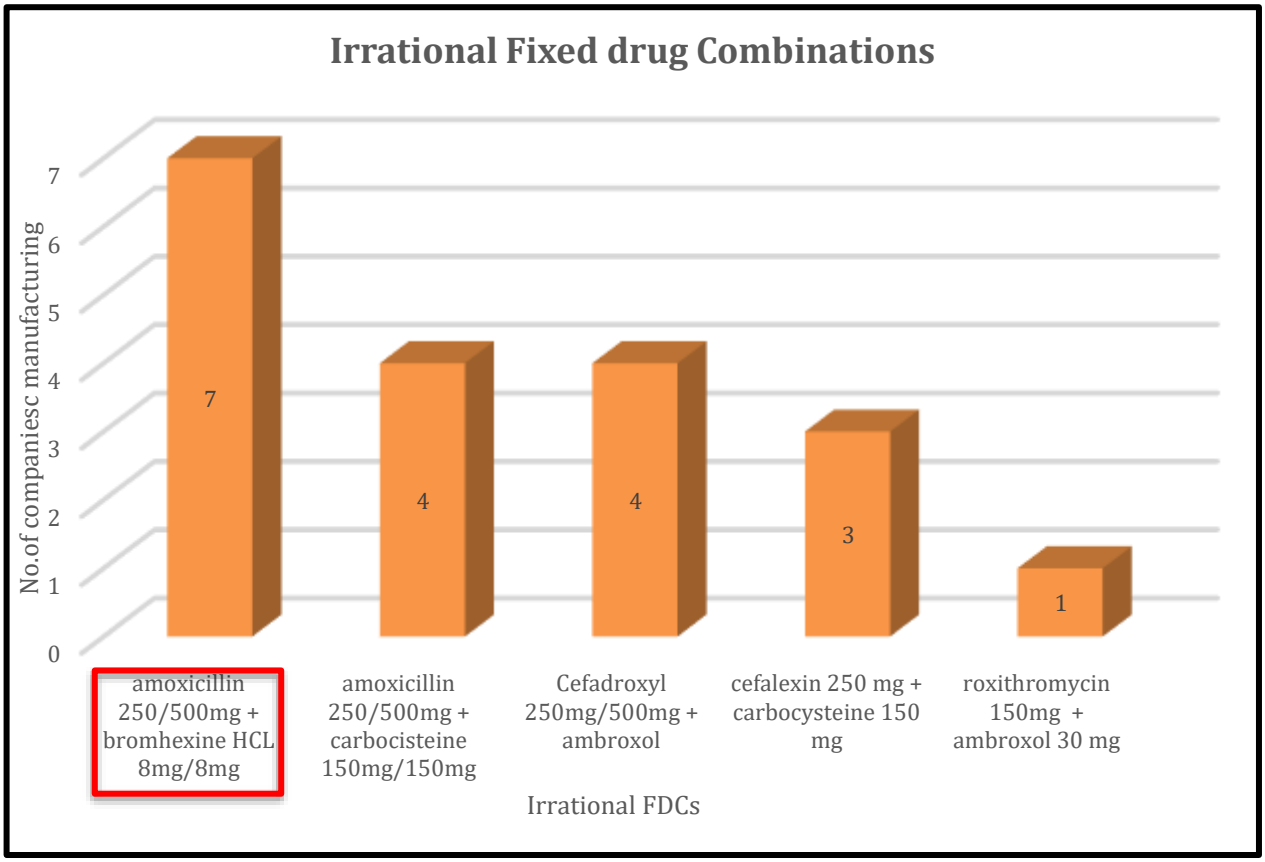


Figure 4: Irrationality due to action of individual drugs on different systems

*The encircled red marked FDCs are the drugs prohibited for manufacture and sale through Gazette notifications under section 26a of drugs & cosmetics Act 1940 by the ministry of health and family welfare[6].

Also, our paper gives an insight about 15 banned FDC drugs which are astonishingly sold and marketed by a number of pharmaceutical companies in the Indian Market. Also ,list of other banned FDCs is given.

Sr.no.	List of antibacterial FDCs prohibited for manufacture and sale through Gazette notifications under section 26a of drugs & cosmetics Act 1940 by the ministry of health and family welfare.	Date of prohibition	No. of companies manufacturing
1.	Fixed Dose Combinations of Ofloxacin + Ornidazole Injection	S.O. 1031 (E) Dated 10.03.2016	
2.	Ofloxacin + Ornidazole suspension		
3.	Roxithromycin + Serratiopeptidase S.O.	S.O. 904 (E) Dated 10.03.2016	1
4.	Amoxicillin+Bromhexine	S.O. 777 (E) Dated 10.03.2016	7
5.	Ofloxacin +Ornidazole +Zinc bisglycinate	S.O. 775 (E) Dated 10.03.2016	130
6.	Amoxycillin +Dicloxacillin +	S.O. 753 (E) Dated 10.03.2016	1
7.	Ofloxacin +Metronidazole	S.O. 767 (E) Dated 10.03.2016	24
8.	Doxycycline +Serratiopeptidase	S.O. 765 (E) Dated 10.03.2016	1
9.	Levofloxacin +Ornidazole +Alpha Tocopherol Acetate	S.O. 761 (E) Dated 10.03.2016	18
10.	Cefpodoxime Proxetil +Levofloxacin	S.O. 759 (E) Dated 10.03.2016	2
11.	Ofloxacin +Nitazoxanide	S.O. 758 (E) Dated 10.03.2016	1
12.	Cefixime +Linezolid	S.O. 756 (E) Dated 10.03.2016	2
13.	Azithromycin + Levofloxacin	S.O. 755 (E) Dated 10.03.2016	1
14.	Azithromycin +Cefpodoxime	S.O. 772 (E) Dated 10.03.2016	4
15.	Azithromycin+Cefixime	S.O. 752 (E) Dated 10.03.2016	5

Here is the list of other banned FDCs :

16.	Azithromycin + Ambroxol	S.O. 757 (E) Dated 10.03.2016
17.	Metronidazole +Tetracycline	S.O. 779 (E) Dated 10.03.2016
18.	Azithromycin + acebrophyline	S.O. 865 (E) Dated 10.03.2016
19.	Azithromycin + ofloxacin	S.O. 763 (E) Dated 10.03.2016
20.	Amoxicillin +Cefixime +Potassium Clavulanic Acid	S.O. 757 (E) Dated 10.03.2016
21.	Cefixime +levofloxacin	S.O. 766 (E) Dated 10.03.2016
22.	Norfloxacin+ Metronidazole + zinc Acetate	S.O. 776 (E) Dated 10.03.2016
23.	Penicillin with sulfonamides,	Dated 23.07.1983
24.	Chloramphenicol with any other drug for internal use	Dated 03.11.1988
25.	Tetracyclines with Vitamin C	Dated 23.07.1983
26.	Anti-Tubercular drugs with Vitamins except Isoniazid with Pyridoxine	GSR NO.578(E) Dated 23.07.1983
27.	Anthelminthics drugs with a Purgative	GSR NO.69(E)Dated 11.02.1991
28.	Streptomycin with penicillin in Parenteral Preparation,	GSR NO.93(E)Dated 25.02.1997
29.	Nitrofurantoin with Trimethoprim	GSR NO.170(E)Dated12.03.2001
30.	Nalixic acid with any anti-amoebic including metronidazole	GSR NO.170(E)Dated12.03.2001

DISCUSSION

Rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.[8]

Fixed dose combinations are products containing two or more ingredients in a Fixed ratio of doses used for a particular indication.[1] Over the time, our Healthcare practice has witnessed an enormous growth in the trend of prescribing FDCs, which is increasing day by day. But today, all these FDCs which are prescribed or consumed by the patients they benefit or also harm? In other words, are these medications rational or irrational?

Today, the consumption of Irrational FDC have become a major problem in the country. More than half of all FDCs available are irrational and their overuse, underuse or misuse results in widespread health hazards.[9] The health hazards comprise of rise to resistant strains of organisms, increasing ADRs, drug interactions, financial burden and many other problems.[10] This study aims to fulfil the

lacuna in the research regarding rational and irrational antibacterial FDCs available in the Indian market.

Firstly, all the antibiotic FDCs available were listed from CIMS 2022, Drug Today Jan-Apr-2022 and Market study. The number of companies producing each combination was also numbered. Their rationality was assessed based on pharmacodynamic properties, pharmacokinetic properties, Drug interactions, WHO Essential List Of Medicines 2021(22nd) list and National List of Essential Medicines (NLEM) 2022. WHO [World Health Organization] list of essential medicines consists of 12 and NLEM Consists of only 3 antibacterial FDCs only.

In our study, a total of 86 combinations available in Indian market were listed and analysed For rationality, assessment was done on the basis of the criterion such as the drugs in the combination act by different mechanisms, the pharmacokinetics must not be widely different, the combination should not have supra-additive toxicity of the ingredients.

More than half of all FDCs analysed were found to be irrational . National List of Essential Medicines consists of only 3 and WHO list of Essential Medicines consists of only 12 antibiotic FDCs but today, more than hundred FDCs are circulated in the market, which are not strictly scrutinized by any authority.

Previous studies were done to assess the rationality of various FDCs. Irrationality of different group of drugs was analysed by several authors (Gautam CS et al,2008) in which 68% were rational while 32% were irrational combinations.[10] Another study evaluated the level of understanding among the dental clinicians and residents about these concepts. (Kopal Sharma et al ,2014)[9]

Irrational, underuse, overuse or misuse of FDCs results in widespread health hazards. The most crucial of the health hazards is the rise of resistant strains of organisms. This leads to drugs becoming ineffective against common infections. Superbugs are microbial strains that have become resistant to the drugs used to treat them. As a result, more potent classes of drugs have to be used which increase the number of side effects for the patient.[12]

Superbugs have caused several hospital-based outbreaks in recent years. Also, Several strains of bacterial superbugs have been found circulating not only in hospitals but also in communities.[12] This poses a major health risk to the population in the near future. The main strains include Methicillin-resistant Staphylococcus aureus (MRSA),Carbapenem-resist Enterobacteriaceae (CRE),Vancomycin-resistant Enterococcus (VRE),Multidrug-resistant Acinetobacter,E. coli H30-RX.[8] Irrational antibiotic FDCs also leads to increasing Adverse drug reactions, drug interactions and ultimately financial burden to the patients.

Here is the list of antibacterial FDCs listed in National List of Essential Medicines (NLEM) 2022 and WHO Essential List Of Medicines 2021(22nd)list.[6]

National List of Essential Medicines (NLEM) 2022	WHO Essential List Of Medicines 2021(22nd)list.
Amoxicillin (A) + Clavulanic acid (B). Tablet 500 mg (A) + 125 mg (B) Oral liquid 200 mg (A) + 28.5 mg (B)/5 mL (p) Dry Syrup 125 mg (A) + 31.25 (B)/ 5 mL (p) Powder for Injection 500 mg (A) + 100 mg (B) Powder for Injection 1 g (A) + 200 mg (B)	125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL [c]. Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt). Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.
Co-trimoxazole [Sulphamethoxazole (A) + Trimethoprim	sulfamethoxazole + trimethoprim Injection: 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule.

(B)]** Tablet 400 mg (A) + 80 mg (B) Tablet 800 mg (A) + 160 mg (B) Oral liquid 200 mg (A) + 40 mg (B)/5 mL (p)	Oral liquid: 200 mg + 40 mg/5 mL. Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.
Piperacillin (A) + Tazobactam (B) Powder for Injection 1000 mg (A) + 125 mg (B) Powder for Injection 2000 mg (A) + 250 mg (B) Powder for Injection 4000 mg (A) + 500 mg (B)	Piperacillin (A) + Tazobactam (B) 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as
	ceftazidime + avibactam(Powder for injection: 2 g + 0.5 g in vial.)
	meropenem + vaborbactam (1 g + 1 g in vial)
	imipenem + cilastatin
	ethambutol + isoniazid + pyrazinamide + rifampicin 275 mg + 75 mg + 400 mg + 150 mg.
	ethambutol + isoniazid + rifampicin
	isoniazid + pyrazinamide + rifampicin
	isoniazid + rifampicin
	isoniazid + rifapentine
	isoniazid + pyridoxine + sulfamethoxazole + trimethoprim

Among the rational FDCs ,the most common FDC was ‘amoxicillin 500mg + clavulanic acid 125 mg’ .It is the combination of B- Lactam antibiotic and B lactamase inhibitor. The B lactamase inhibitors inhibit plasmid mediated B lactamases produced by bacteria which are responsible for transferred drug resistance.[8] Thus they enhance the antibiotic activity .
The most common irrational FDC which combines bacteriostatic with bacteriocidal actions is cefixime 200mg + azithromycin 500mg. This combination is irrational because the bactericidal antibiotic (cefixime) kills actively growing bacteria; inclusion of a bacteriostatic antibiotic can arrest this growth and thus, prevent the killing by the bactericidal antibiotic. Therefore, this combination doesn’t help each other but instead decreases each other efficiency.[11]

Another combination of antibiotic and antiparasitic is irrational. The most common irrational FDC which combines antibiotic and antiparasitic drug was found to be ’ofloxacin400mg plus ornidazole 500mg’ . This combination is irrational because usually a single causative organism; either bacteria or parasite is responsible for causing diarrhoea and mixed infection occurs rarely.[12] So, this will lead to unnecessary adverse effects, additional cost and ultimately leading to increasing resistance.
Another group of irrational FDCs include individual drugs from the same class acting through same mechanism.The most common Irrational FDC found in this group was of amoxicillin 250 mg +cloxacillin 250mg’ They have no superadded benefit but if given together,will add to toxicity and bacterial resistance of the drugs.[12]

Another group consists of medication whose Irrationality is based on action of individual drugs on different systems. The most common Irrational FDC found in this group was of ‘amoxicillin 500mg +bromhexine 8 mg’.Antibiotic plus mucolytic agent is used to liquefy thick respiratory secretions. There is no need of combining mucolytic agent with antibacterial, as thick secretions in respiratory tract are not always due to bacterial infections. Therefore, these FDCs are irrational.[12]

We also found out that a large number of FDCS are being sold by several companies despite their prohibition from CDSCO seven years ago. The FDC of Ofloxacin + Ornidazole is not only marketed but sold by 130 companies! and adding the group consisting of lactobacillus ,the number goes upto

146 companies. Similarly, the banned Ofloxacin + Metronidazole combination is sold by 24 companies. Another banned combination Levofloxacin +Ornidazole is sold by 18 companies.
Over the years the Indian Drug Control Authority has issued banned notifications on many FDCs like Ofloxacin + Ornidazole suspension, Ofloxacin +Metronidazole; Order S.O. 767 (E)
Dated 10.03.2016 and many more.
But these measures have not been effective to deter manufacturers from selling the irrational FDCs and also manufacturing new combinations. Companies continue to produce irrational combinations with vigor in order to reap the benefits of huge sales in the market. But their administration to patients is unethical and can be harmful to them in the future.

CONCLUSION

Our study concludes that a huge number of Irrational as well as banned FDCs are being supplied in the Indian market by different companies. Thus, awareness about irrational FDCs of antibacterial drugs is will help to limit the spread of drug resistance will be beneficial for the future of a resource poor country like India. the unethical distribution of FDCs among the patients. which Hence, a strict review of a regulatory framework for FDC manufacturing, marketing and scrutiny of circulating drugs is needed for the betterment of patient care in the country.

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