ANTIBIOTIC POTENTIATORS (multidrug pump inhibitors) FROM PLANTS

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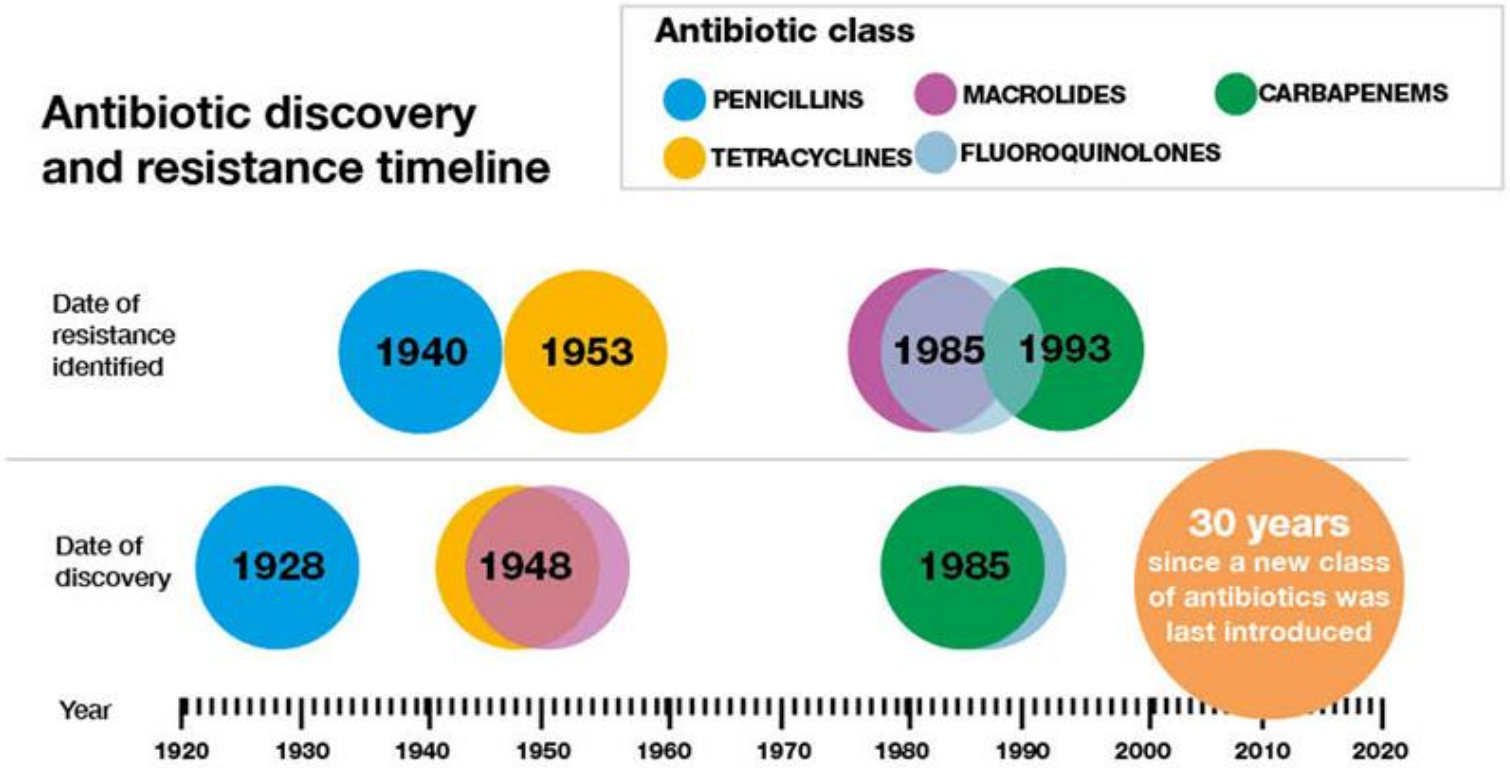
Present scenario & Need

- 2 or 3 antibiotic variants launched every year
- Increasing resistance
- Increasing infective ailments/agents
- Anti-infective agents expected to increase 60%
- New sources required

Antibiotic discovery



From Wockhardt

- Dr. Mahesh Patel, director of drug discovery research at Wockhardt, says the biggest barrier for companies is the regulatory burden. “The costs of trials are so high and society is not willing to pay the high price for antibiotics; so that is the paradox. Society wants a cheaper antibiotic, but the costs of development will be high. So we need to manage these two conflicting needs.”

Hospital related infectionS

- 5-10% in developed countries
- 10-30% IN DEVELOPING COUNTRIES
- Rates vary between countries, within the country, within the districts and sometimes even within the hospital itself, due to

    1) complex mix of the patients

    2) aggressive treatment

    3) local practices

Incidence

- Average Incidence - 5% to 10%, but maybe up to 28% in ICU
- Urinary Tract Infection - usually catheter related -28%
- Surgical Site Infection or wound infection -19%
- Pneumonia -17%
- Blood Stream infection - 7% to 16%

Do you know?

- Nosocomial infections in ICU
- Longer the duration, higher the chances of infections
- 45% of patients are infected
- 25% of them die due to infections only

Nosocomial infections

- Penumonia
- Lower respiratory tract infection
- Urinary tract infection
- Bloodstream infection
- Microorganisms include
  - Enterobacteriaceae
  - *Staph aureus*
  - Coagulase negative staphylococci
  - *Acinetobacter baumanii*

Asian Heart Institute (AHI)

Dr. Vijay D'Silva, Director, Critical care,

"Suggestions to strengthen the infection control programme is turned down by the management of most hospitals as spending on infection control does not generate revenue."

Few quotes from Pharma experts

- Günter Wess from Aventis said: "Most of the molecules that are chemically optimized are biologically not relevant. We have moved away too far from the science of drug discovery to industrialization."
- Stuart Schreiber from Harvard University, on the other hand, blamed "the risk-adverse attitude of big pharma" for much of the trouble: "They are all going for the same targets, and then wonder why they cannot find any not more".

SINGLE VOLUNTEER STUDY

- Head injured ICU patient was infected with MDR respiratory pathogen *Acinetobacter baumanii and* was treated with two antibiotics imipenem and ceftriaxone with no improvement for 3 weeks in a reputed hospital in Bangalore
- A pure plant compound “Z” given in 200µg per day with the above antibiotics through the stomach tube improved his condition and got relieved of the infection in 5 days
- Plate assay also revealed dose dependant excellent clearing zone with plant compound in the presence of 30µg ceftriaxone & 10µg imipnem disc separately

2nd study

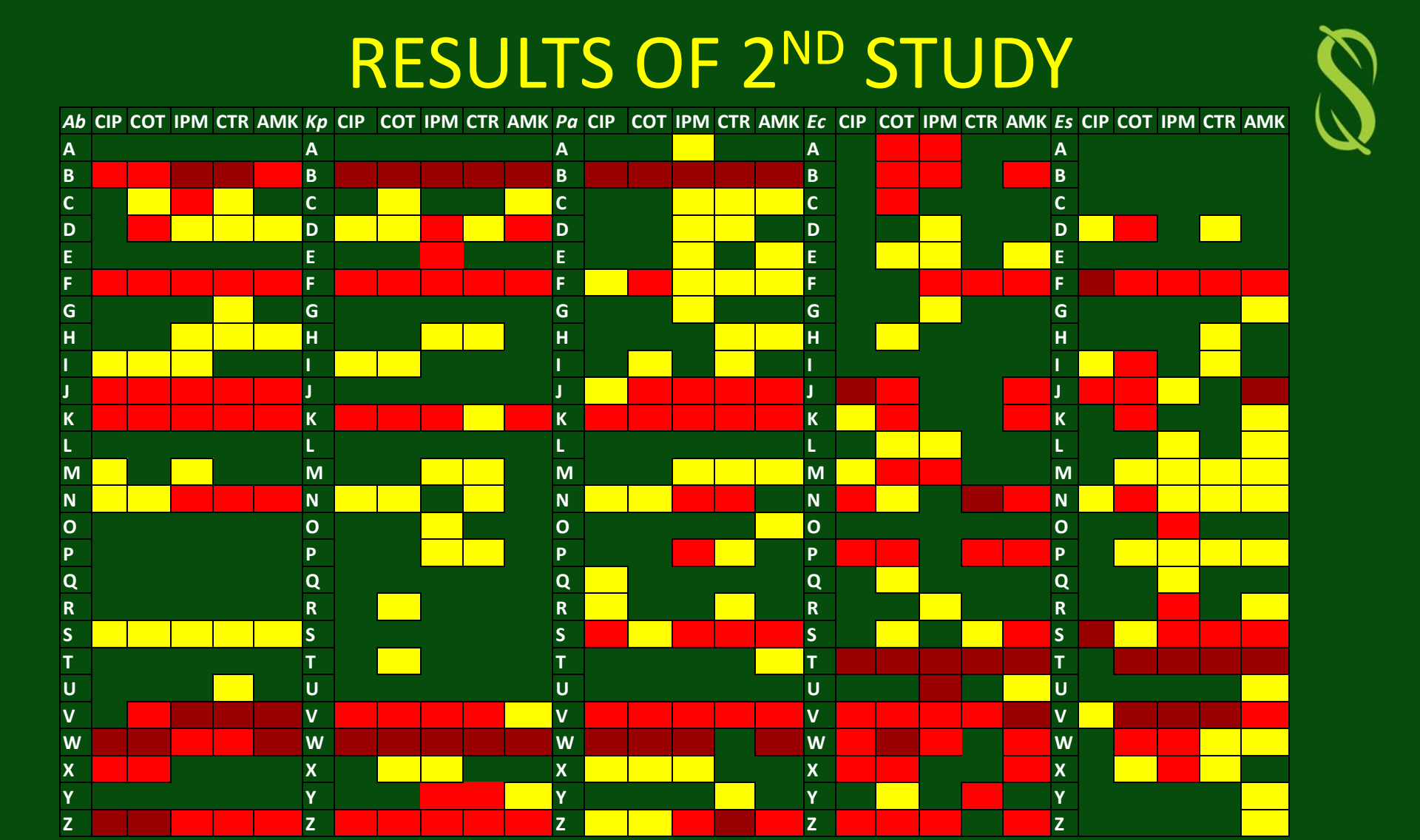
- 5 Clinically relevant MDR pathogen were selected
- They were resistant to 3 or more antibiotics, Amikacin, Imipenem, Ceftriaxone, Cotriamoxazole and Ciprofloxacin
- 25 plant extracts were screened in disk diffusion assay
- 6 extracts and 1 compound showed positive results

Pathogens vs MDR vs Antibiotics

Acinetobacter	*Klebsiella*	*Escherichia*	*Pseudomonas*	*Enterococcus*
RND	RND	RND	RND	
MATE	MATE	MATE	MATE	
MFS	MFS	MFS	MFS	MFS
SMR & PACE	SMR	SMR	SMR	
ABC	ABC	ABC	ABC	ABC

Antibiotic	Group	MDR category
Ceftriaxone	Cephalosporin	ABC, RND
Amikacin	aminoglycoside	RND, MATE
Cotriamoxazole	sulfonamide	SMR
Ciprofloxacin	fluroquinolone	RND, MFS, MATE
Imipenem	beta lactam	RND, MFS

RESULTS OF 2ND STUDY



Moderately effective with resp antibiotics

Highly effective with resp antibiotics

Extremely effective with resp antibiotics

CIP=Ciprofloxacin (fluroquinalone)

IMP=Imipenem (β-lactam)

AMK=Amikacin (aminoglycoside)

COT=Cotriamoxazole (sulfonamide)

CTR= Ceftriaxone (cephalosporin)

A to Y = 25 plant extracts

Z = Pure palnt compund

Ab= *Acinetobacter baumanii* ***Pa=*** *Pseudomonas aeruginosa* ***Kp=*** *Klebsiella pneumoniae* ***Ec=*** *Escherichia coli* ***Es=*** *Enterococcus sp*

OUR RESEARCH LED US TO BELIEVE

- Selection of proper plant for the study is more important in getting desired result
- A plant extract / compound can potentiate one or more antibiotic specific to one pathogen
- Increased concentration of plant extracts have higher efficiency of potentiation
- Extract B, J, K, T, V, W and compound Z potentiate higher than other extracts
- Extract B & W for *K. pneumoniae* & *P. aeruginosa,* V & W for *A. baumanii* and T & V for *E. coli* & *Enterococcus* sp did exceedingly well with different classes of antibiotics

Inhibitors – Present stage in the world

- No biochemical data on direct interaction of any inhibitor with any efflux protein has been proved
- No inhibitor has been licensed for human or even veterinary