ORIGINAL RESEARCH

SCREENING OF ANTIMICROBIAL EFFECT OF SOME NON-ANTIBIOTICS (ANTI-HYPERTENSIVE) AGAINST SOME SELECTED MICROORGANISMS

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ABSTRACT:

Antibiotics are most important series of drugs which are use over a large numbers of microbial infections, but in todays practice use of antibiotics in a desperate way creates its resistance in human physiological system and continuously narrow it's theraputic range. Despite their use is becoming increasingly restricted. The reason behind such a rapid decline is largely attributed to the development of drug resistance among microorganisms. Such a phenomenon is coupled by the toxicity possessed by many antimicrobials. For this taking in mind present scenario The aim of this study was to screen the antimicrobial activity of non-antibiotic drugs like antihypertensives. Calcium channel blockers like verapamil and beta blockers like propranolol showed highest activity for *S.aureus* and *B.subtilis* respectively. While ACE inhibitors like enalapril and ARBs like losartan showed highest activities for *V.cholerae* and *S.typhii* respectively.

KEYWORDS: Antimicrobial activity, anti hypertensives, agar well diffusion.

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INTRODUCTION:

A variety of pharmaceutical preparations, which are applied in the management of non-infectious diseases, have shown in vitro some antimicrobial activity. These drugs are called "non-antibiotics". So far, a lot of attention has been focused on phenothiazines, thioxanthenes and other agents with affinities to cellular transport systems or agents showing other inhibition mechanism. Several authors confirmed that some non-antibiotics are "helper compounds", which enhance the in vitro activity of certain antibiotics against specific bacteria (ex. omeprazole and nizatidine enhance the effect of metronidazole on Helicobacter pylori).

Such an effect has been noticed for barbiturates, beta-adrenergic receptor antagonists, diuretic drugs, H1 antihistamines, mucolytic agents, nonsteroid anti-inflammatory drugs, proton pump inhibitors and psychotherapeutic drugs. Synergic or antagonistic effects with antibiotics of several of these drugs have also been noticed.[1]

The aim of this study was to screen the antimicrobial activity of non-antibiotic drugs like antihypertensive.

Antibiotics and antimicrobial chemotherapeutics exist in large numbers in today's pharmaceutical market. Despite their use is becoming increasingly restricted. The reason behind such a rapid decline is largely attributed to the development of drug resistance among microorganisms. Such a phenomenon is coupled by the toxicity possessed by many antimicrobials. Multiple drug resistance among highly infective microorganisms generates a major obstacle to clinical applications in recent years. As development of a new broad range antimicrobial agent is difficult and takes several years, increasing the activity of existing antibiotics would be a future solution to this challenge. However, there is a search for newer antimicrobial agents that can overcome these drawbacks. Studies in this line have exposed the fact that several compounds, belonging to various pharmacological classes, possess moderate to powerful antibacterial activity.There are some synthetic or natural medicinal compounds, referred as non-antibiotics, which are effective against microbial metabolism. A number of non-antibiotic drugs including non-steroidal anti-inflammatory drugs, calcium channel blockers and antidepressants have been reported to display biocidal or biostatic activity. In addition, recent studies showed that some repellent molecules such as Picaridin and DEET, which are spread to the body of people and clothes to remove some arthropods (mosquitoes, lice, ticks, etc.), have also antimicrobial property. [11,12]

These non-antibiotic drugs act in different manners on microbial growth. They may have direct antimicrobial activity (antimicrobial nonantibiotics), increase the efficiency of an antibiotic as given together (helper compounds), or change the pathogenicity of microorganisms or activity on the physiology such as modulating macrophage activity. For example, antidepressants such as Sertraline, Paroxetine, and Fluoxetine have been shown to decrease minimum inhibition concentration (MIC) levels of several antibiotics mainly by inhibiting efflux pump activity. Beyond acting synergistically, some psychotic drugs exhibit antimicrobial characteristics. They have been effective against gram negative and positive bacteria, yeast, fungi, and protozoa. [9,11]

The main limiting factor of non-antibiotic drugs to display their antimicrobial characteristics in mammalian system is that the maximum serum level remains (approx. 1mg/L) lower than the concentration required inhibiting microbial growth. However, these levels might be sufficient to modify microbial metabolism and act synergistically with certain antibiotics. For example, it has been claimed that 0.75mg/L sertraline, lower than the tissue concentration in vivo, resulted in lack of hyphal transformation and decrease in virulence for Candida spp. Given the increasing incidence of infections and the limited efficacy of currently available antimicrobial agents, new approaches are needed.[13,14]

A broad spectrum of drugs produced by microorganisms might be investigated for their antimicrobial activity. On the other hand, the currently published information describes in vitro activity and in vivo efficacy in animals. There is very limited clinical information that indicates clinically relevant activity of non-antibiotics compounds in humans. In addition, there is a need to take pharmaco dynamics into account in vivo. On the basis of this information, new approaches to the infection can be designed.[4,5]

Amongst range of non-antibiotics, there are inconclusive reports of antihypertensives being reported as non-antibiotics. Anti hypertensives have served as an important treatment modalities in patients with hypertension associated with elevated diastolic pressures, in whom therapy reduces morbidity and mortality from cardiovascular disease. Effective antihypertensive therapy markedly reduces the risk of strokes, cardiac failure, and renal insufficiency due to hypertension. However, reduction in risk of myocardial infarction may be less impressive.

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age; for example, about 50% of people between the ages of 60 and 69 years old have hypertension, and the prevalence is further increased beyond age 70.

Hypertension is defined conventionally as a sustained increase in blood pressure ≥140/90 mm Hg, a criterion that characterizes a group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention. Actually, the risk of both fatal and nonfatal cardiovascular disease in adults is lowest with systolic blood pressures of less than 120 mm Hg and diastolic BP less than 80 mm Hg; these risks increase progressively with higher systolic and diastolic blood pressures.[6]

Principles of Antihypertensive Therapy:

Non-pharmacological therapy is an important component of treatment of all patients with hypertension. In some stage 1 hypertensives, blood pressure may be adequately controlled by a combination of weight loss (in overweight individuals), restricting sodium intake, increasing aerobic exercise, and moderating consumption of alcohol. These lifestyle changes, though difficult for many to implement, may facilitate pharmacological control of blood pressure in patients whose responses to lifestyle changes alone are insufficient. Arterial pressure is the product of cardiac output and peripheral vascular resistance. Drugs lower blood pressure by actions on peripheral resistance, cardiac output, or both. Drugs may reduce the cardiac output by inhibiting myocardial contractility or by decreasing ventricular filling pressure. Reduction in ventricular filling pressure may be achieved by actions on the venous tone or on blood volume via renal effects. Drugs can reduce peripheral resistance by acting on smooth muscle to cause relaxation of resistance vessels or by interfering with the activity of systems that produce constriction of resistance vessels (e.g., the sympathetic nervous system).[8]

Table 1: Classification of Antihypertensive Drugs by Their Primary Site or Mechanism of Action:[15]

Diuretics	**1.** Thiazides and related agents (hydrochlorothiazide, chlorthalidone, *etc*.)
	2. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)
	3. K+-sparing diuretics (amiloride, triamterene, spironolactone)
Sympatholytic drugs	1.Beta Adrenergic antagonists (propranolol, atenolol, *etc*.)
	2. Alpha Adrenergic antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine)
	4. Centrally acting agents (methyldopa, clonidine, guanabenz, guanfacine)
	5. Adrenergic neuron blocking agents (guanadrel, reserpine)

Ca2+ channel blockers	verapamil, diltiazem, nimodipine, felodipine, nicardipine, isradipine, amlodipine
Angiotensin converting enzyme inhibitors	captopril, enalapril, lisinopril, quinapril, ramipril, benazepril, fosinopril, moexipril, perindopril, trandolapril
Angiotensin II–receptor antagonists	losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan
Vasodilators	**1.** Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
	2. Arterial and venous (nitroprusside)

SOME ANTIHYPERTENSIVE DRUGS: [15]

PROPRANOL

Propranolol is a medication of the beta blocker type. It is used to treat high blood pressure, a number of types of irregular heart rate, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors. It is used to prevent migraine headaches, and to prevent further heart problems in those with angina or previous heart attacks. It can be taken by mouth or by injection into a vein. The formulation that is taken by mouth comes in short acting and long acting versions. Propranolol appears in the blood after 30 minutes and has a maximum effect between 60 and 90 minutes when taken by mouth.

Propranolol dosing information:

Table 2: Usual Adult Dose of Propranolol for Hypertension:

Initial dose:	Immediate-release: 40 mg propranolol orally 2 times a day
	Sustained-release: 80 mg orally once a day
	XL sustained-release: 80 mg orally once a day at bedtime
Maintenance dose:	Immediate-release: 120 to 240 mg orally per day
	Sustained-release: 120 to 160 mg orally per day
	XL sustained-release: 80 to 120 mg orally once a day at bedtime
Maximum dose:	IR/SR: 640 mg orally per day
	XR: 120 mg orally per day

Effective plasma concentration between 10 – 100 mg/l

SOLUBILITY

- Soluble in water and in ethanol (95%).
- Slightly soluble in chloroform
- Practically insoluble in ether.

VERAPAMIL

Verapamil is a calcium channel blocker. It works by relaxing the muscles of your heart and blood vessels. Verapamil is used to treat hypertension (high blood pressure), angina (chest pain), and certain heart rhythm disorders. Verapamil may also be used for purposes not listed in this medication guide.

DOSAGE:

Table 3: Extended release capsules

Initial dose	200 mg orally once a day at bedtime (usual dose in clinical trials); in rare cases, initial doses of 100 mg orally once a day at bedtime may be warranted in patients who have an increased response to verapamil (e.g., low-weight patients)
Maintenance dose	Upward titration should be based on therapeutic efficacy and safety evaluated about 24 hours after dosing. If adequate response is not obtained with the initial dose, it may be titrated upward.
Maximum dose	400 mg/day

Table 4: Extended release tablets

Initial dose	180 mg orally once a day at bedtime
Maintenance dose	If adequate response is not obtained with the initial dose, it may be titrated upward.
Maximum dose	480 mg/day

Blood or plasma concentrations are usually in a range of 50 – 500 µg/l in persons on therapy with that drug. But may rise to 1 – 4 mg/l in acute overdose patients and are often at levels of 5 – 10 mg/l in fatal poisonings.

SOLUBILITY:

- Freely soluble in chloroform
- Soluble in water
- Sparingly soluble in ethanol (95%)

ENALAPRIL

Enalapril is an ACE inhibitor. ACE stands for angiotensin converting enzyme. Enalapril is used to treat high blood pressure (hypertension) in adults and children who are at least 1 month old. Enalapril is also used to treat congestive heart failure in adults. Enalapril is also used to treat a disorder of the ventricles (the lower chambers of the heart that allow blood to flow out of the heart). This disorder can decrease the heart's ability to pump blood to the body.

Table 5: DOSAGE:

Initial dose (oral tablets or solution):	5 mg orally once a day
Maintenance dose (oral tablets or solution):	10 to 40 mg orally per day as a single dose or in 2 divided doses
Maximum dose:	40 mg orally daily as a single dose or in 2 divided doses

Plasma concentration: 5 – 200 ng/ml

Solubility :

- Freely soluble in methanol and dimethylformamide
- Soluble in ethanol (95%)
- Sparingly soluble in water

LOSARTAN:

Losartan belongs to a group of drugs called angiotensin II receptor antagonists. It keeps blood vessels from narrowing, which lowers blood pressure and improves blood flow. Losartan is used to treat high blood pressure (hypertension). It is also used to lower the risk of stroke in certain people with heart disease. Losartan is used to slow long-term kidney damage in people with type 2 diabetes who also have high blood pressure. Losartan may also be used for purposes not listed in this medication guide.

Table 6: DOSAGE:

Initial dose:	50 mg orally once a day
Maintenance dose:	25 to 100 mg orally per day in 1 or 2 divided doses

Plasma concentration: 10 – 300 ng/ml
Solubility:

- Freely soluble in water
- Sparingly soluble in isopropyl alcohol.

RESEARCH METHODOLOGY:

Screening for antimicrobial Activity:

An antimicrobial is an agent that kills microorganisms or inhibits their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungals are used against fungi. They can also be classified according to their function. Agents that kill microbes are called microbicidal , while those that merely inhibit their growth are called biostatic. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis.

The MIC(Minimal Inhibitory Concentration) of a bacteria to a certain antimicrobial agent gives a quantitative estimate of the susceptibility. MIC is defined as the lowest concentration of antimicrobial agent required to inhibit the growth of the organism. The principle is simple: agar plates ,tubes microlitre trays with two-fold dilutions of antibiotics are inoculated with a standardised inoculums of the bacteria and incubated under standardised conditions following NCCLS guidelines. The next day, the MIC is recorded as the lowest concentration of antimicrobial agent with no visible growth. The MIC informs us about the degree of resistance and might give you important information about the resistance mechanism and the resistance genes involved[2].

Two general methods are usually employed for microbiological assay, the cylinder-plate (or cup-plate) method and the turbidimetric (or tube assay) method.

The cylinder-plate method (Method A) depends upon diffusion of the antibiotic from a vertical cylinder through a solidified agar layer in a Petri dish or plate to an extent such that growth of the added micro-organism is prevented entirely in a zone around the cylinder containing a solution of the antibiotic. The turbidimetric method (Method B) depends upon the inhibition of growth of a microbial culture in a uniform solution of the antibiotic in a fluid medium that is favourable to its rapid growth in the absence of the antibiotic.

The assay is designed in such a way that the mathematical model on which the potency equation is based can be proved to be valid. If a parallel-line model is chosen, the two log dose response lines of the preparation under examination and the standard preparation should be parallel; they should be rectilinear over the range of doses used in the calculation. These conditions should be verified by validity tests for a given probability. Other mathematical models, such as the slope ratio method, may be used provided that proof of validity is demonstrated.[3,4]

Procurement of the commercially available Drugs.

The following drugs were obtained commercially from registered drug stores:

- verapamil hydrochloride from Abott Healthcare Pvt. Ltd.
- Propranolol hydrochloride from Cipla LTD.
- Enalapril malate from Dr. Reddy's Laboratories LTD.
- Losartan tablet IP from Unichem Laboratories LTD

Procedure

The assay procedure followed was agar well diffusion method.
The entire process consists of the following steps:

a) Preparation of media
b) Preparation of buffer
c) Adjusting the media using the buffer
d) Preparation of standard antibiotic solution
e) Preparation of sample solution
f) Test organism selection
g) Preparation of innoculation
h) Determination of innoculation
i) Determining the zone of inhibition of bacterial growth in each petridishes

Preparation of culture media

- Peptone-1%,
- Beef-0.5%,
- NaCl-0.5%,
- Agar-2%

- pH-7.2-7.4

- Accurately weighed constituents for preparation of 100 ml nutrient agar media were taken in batches of 400 ml were prepared accordingly.
- The pH was adjusted using 0.1 N NaOH solutions & then distributed into McCartney bottle and then sterilized.

Preparation of standard antibiotic solution

Erythromycin in the concentration of 1000mcg/ml was prepared and considered as standard antibiotic solution.

Preparation of sample solution

Test solutions were serially diluted to obtained different concentrations in correspondence with the attainable therapeutic plasma concentration ranges as obtained from various literature searches.

Table7: Concentrations used:

1	Propranolol	25 mg/l	50 mg/l	75 mg/l	100 mg/l
2	Verapamil	100 µg/l	200 µg/l	300 µg/l	400 µg/l
3	Enalapril	50 ng/ml	100 ng/ml	150 ng/ml	200 ng/ml
4	Losartan	50 ng/ml	100 ng/ml	200 ng/ml	300 ng/ml

Selection of test organism

For this experimental purpose, *S. aureus* ATCC-29157, *S.typhii* C-2114/D7372, *B.subtilis* UC-564, *V.cholerae* 2080 were obtained. Strains of microorganism are collected from Department o Microbiology, Bengal School of Technology.

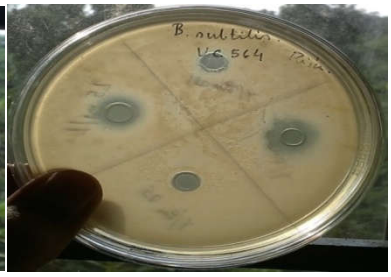
Assay procedure:

- Solutions of test samples were evaluated for antibacterial activity against several gram positive and gram negative organisms.
- The antibacterial activity of sample solutions was performed using cup-plate method.
- Gram positive & gram negative organisms were innoculated into the 20 ml of sterile nutrient agar medium.
- The plate/petridish was virtually divided into 4 equal quadrants.
- Then this medium was poured into the petridish and allowed to solidify.
- Each cylinder was kept on the each quadrant.
- Then different concentrations of test solution were added to the cylinders.
- Then they were incubated at 37 °C for 24 hours.
- The presence of definite zone of inhibition of any size around the cup indicated antibacterial activity.
- The diameter of the zone of inhibition was measured and noted.

RESULT:

Table 8: Propranolol

Organisms	Zone of Inhibition at different Concentrations				STANDARD
	25 mg/l	50 mg/l	75 mg/l	100 mg/l	
S.aureus	11.2 mm	13.2 mm	12.1 mm	11.1 mm	17.6 mm
V.cholerae	11.1 mm	12.6 mm	13.2 mm	9.2 mm	19.2mm
S.typhii	8.2 mm	9.1 mm	9.1 mm	8.1 mm	17.1 mm
B.subtilis	14.1 mm	10.2 mm	15.2 mm	12.1 mm	14.9 mm

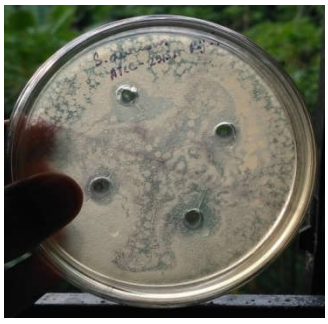
S. aureus *B. subtilis*


V. cholerae *S. typhi*

Fig I: Zone of Inhibition of Propranolol

Table 9: Verapamil

Organisms	Zone of Inhibition at different Concentrations				STANDARD
	100 µg/l	200 µg/l	300 µg/l	400 µg/l	
S. aureus	15.2 mm	13.1 mm	12 mm	14.2 mm	17.6 mm
V. cholerae	10.1 mm	11.2 mm	11 mm	10.1 mm	19.2mm
S. typhii	9.1 mm	11.3 mm	12.1 mm	14.3mm	17.1 mm
B. subtilis	10.2 mm	11.1 mm	11.2 mm	12.2mm	14.9 mm



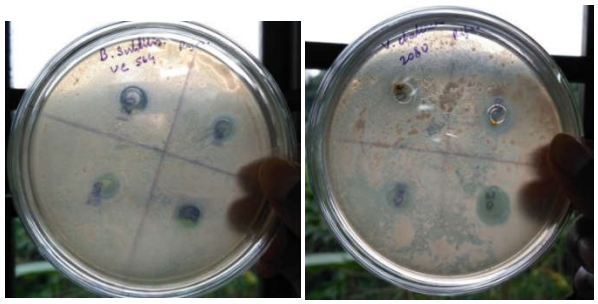

S. aureus *S. typhii*

V. cholerae *B. subtilis*

Fig II: Zone of Inhibition of Verapamil

Table 10: Enalapril

Organisms	Zone of Inhibition at different Concentrations				STANDARD
	50 ng/ml	100 ng/ml	150 ng/ml	200 ng/ml	
S.aureus	14.1 mm	14.4 mm	13.2 mm	12.6 mm	17.6 mm
V.cholerae	10.2mm	9.1 mm	15.1 mm	13.3 mm	19.2mm
S.typhii	15.1 mm	13.1 mm	11 mm	10.8 mm	17.1 mm
B.subtilis	10.1 mm	13.2 mm	12 mm	11.9 mm	14.9 mm



B. subtilis *V. cholerae*

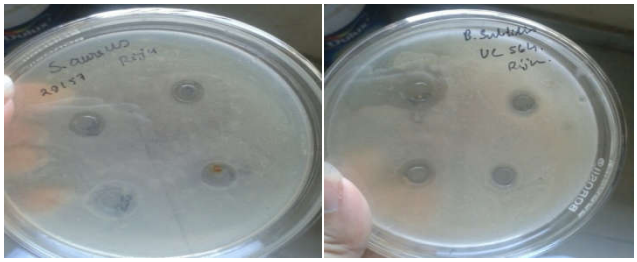
S. typhii *S. aureus*

Fig III: Zone of Inhibition of Enalapril

Table 11: LOSARTAN

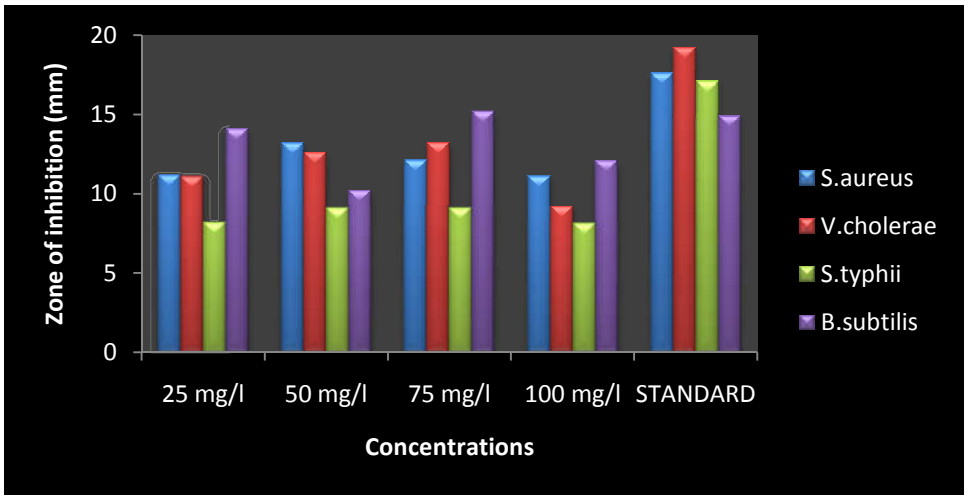
Organisms	Zone of Inhibition at different Concentrations				STANDARD
	50 ng/ml	100 ng/ml	200 ng/ml	300 ng/ml	
S.aureus	12.2 mm	10.6 mm	9.2 mm	11.1 mm	17.6 mm
V.cholerae	12 mm	13.1 mm	14.1 mm	12.5 mm	19.2mm
S.typhii	10 mm	15 mm	12.3 mm	14.1 mm	17.1 mm
B.subtilis	13.1 mm	13.2 mm	13.4 mm	13.2 mm	14.9 mm

V. cholerae *S. typhii*

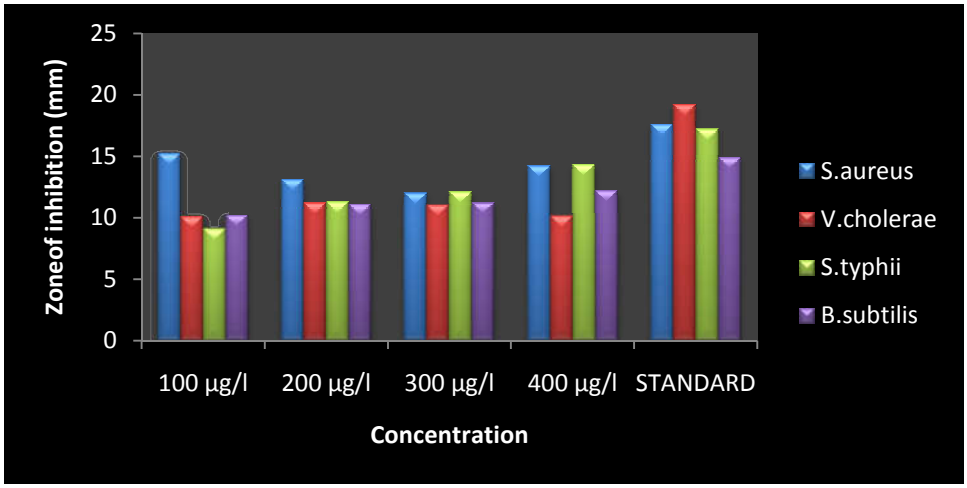


S. aureus *B. subtilis*

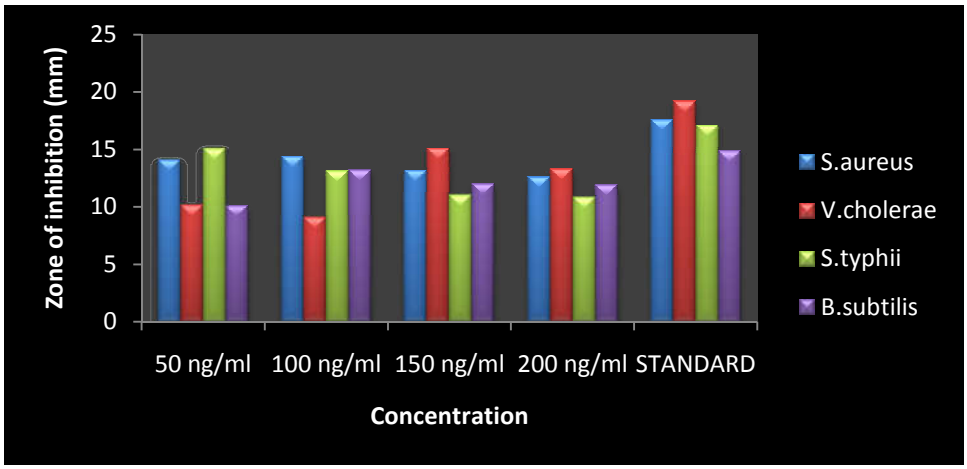
Fig IV: Zone of inhibition of Losartan



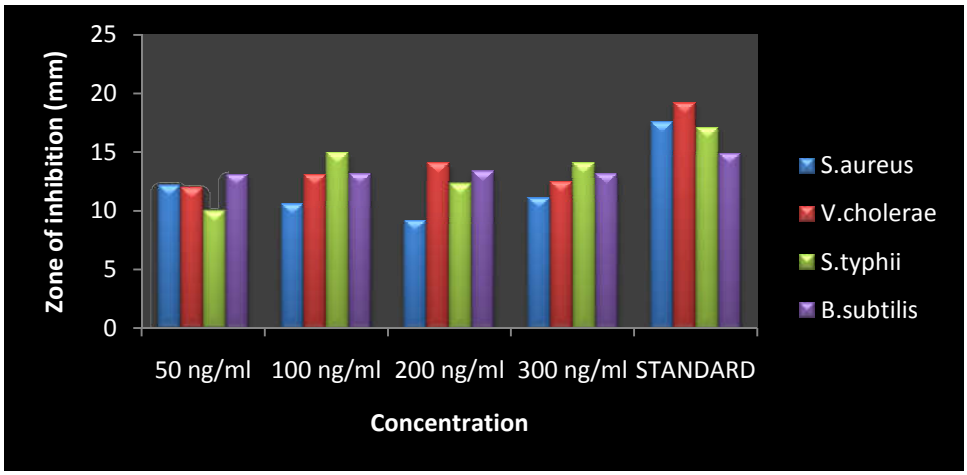
Graph 1: Zone of inhibition of propanolol



Graph 2: Zone of inhibition of verapamil



Graph 3: Zone of inhibition of Enarapril



Graph 4: Zone of inhibition of Losatan

DISCUSSION:

The present study was designed to screen the antibacterial efficacies of some non-antibiotic drugs such as antihypertensives. The study revealed that antihypertensive drugs such as Propranolol, Enalapril, Losartan and Verapamil, each being protoptype of various classes of antihypertensive drugs, in various concentrations showed potential antibacterial effects. These antibacterial effects were mainly demonstrated as zone of inhibitions. Calcium channel blockers like verapamil and beta blockers like propranolol showed highest activity for S.aureus and B.subtilis respectively. While ACE inhibitors like enalapril and ARBs like losartan showed highest activities for V.cholerae and S.typhii respectively.

The study shows potential scopes of future research on this background. Antibacterial effects of non-antibiotics can help fight against microbial resistance in present scenario for this use of antibiotic can control in future and antibiotic resistance may control in human being.

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