

Targeting Antibiotic Resistant *Salmonella enterica*: Bio-matrix Based Selection and Bioactivity Prediction of Potential Nutraceuticals

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Abstract

Aim: Potential herbal leads as novel therapeutic alternatives against Multi-Drug Resistant *Salmonella enterica* serovar typhimurium were investigated and validated by mol inspiration.

Methodology: The present study utilizes an *in silico* 'Herbal Informatics' model which deploys dynamic search protocols, priority indexing and systemic categorization for rationale based selection of nutraceuticals targeting the critical virulence factors of Multi-Drug Resistant *Salmonella enterica* serovar typhimurium. Furthermore, *in silico* biochemical activity prediction was conducted using 'Mol inspiration' cheminformatics tool, so as to propose the drug likeliness of selected natural plant products.

Results: Out of the 05 selected bioactivity parameters of *Salmonella enterica*, lipo-polysaccharide inhibition exhibited maximum relevance as physiological target i.e., 65%, followed by other parameters like enterochelin inhibition, Type III secretory system inhibition, Superoxide dismutase inhibition and Symptomatic relief provision. The binary matrix analysis of database of 50 plants identified using classical bioprospection filtered 28 herbals which exhibited probable potential to mitigate 03 or more virulence factors. The weightage matrix analysis further scrutinized the selection upto 10 herbals having a score more than median weightage matrix score i.e., 14.98. The optimization of data on a scale of 0-1 using fuzzy score matrix analysis led to the final selection of 10 herbals i.e., *Abrus precatorius*, *Azadirachta indica*, *Camellia sinensis*, *Holarrhena antidysenterica*, *Andrographis paniculata*, *Adhatoda vasica*, *Euphorbia hirta*, *Ocimum sanctum*, *Terminalia arjuna* and *Terminalia bellerica*. *In silico* Bioactivity prediction analysis of predominant phytoconstituents of selected herbals revealed *Holarrhena antidysenterica* (Conessine), *Andrographis paniculata* (Andrographolide), *Euphorbia hirta* (Amyrin) and *Terminalia arjuna* (Arjunolic acid) exhibiting drug likeliness with their targeted action as a GPCR Ligand, Nuclear Receptor Ligand or Protease inhibitor.

Keywords: Herbal Informatics; Biochemical activity; Cheminformatics; Nosocomial; *Salmonella enterica* serovar typhimurium; Antibiotic resistance

Introduction

Natural Plant Products (NPPs) with medicinal potential, derived from either traditional or modern medicine, serves as a source of approx. 5000 compounds per species to fight against multifarious diseases. Such tremendous source of secondary plant metabolites employs to defend themselves against bacteria, fungi or viruses and can be used in almost the same way in medicine to treat microbial or viral infections [1]. The effective management of re-emerging pathogens with enhanced scope of attack and attributable resistance require intensive efforts in this direction. NPPs have become an ideal alternative to be explored for their therapeutic utilities by the virtue of their holistic broad spectrum activity; limited or no side effects; better acceptability and ease of local availability [2]. However, the Indian subcontinent has only 2% global market share of herbal medicine despite having 7000 Ayurvedic, 700 Unani, 600 Siddha medicines and 30 modern medicines. This clearly indicates the lack of directed research in instigating the search for newer antimicrobials based on either reverse pharmacology or classical quest of lead moiety. The expected market for NPPs is \$5 Trillion by 2050; if focused research is triggered so as to yield therapeutic leads [3]. Such focused research demands an in depth knowledge of pathophysiology of disease causing microorganisms and rationale based selection of holistic agents having bio-protective potential.

Re-emerging strains of commensal microorganisms e.g., *Salmonella enterica* are scourging the human population due to greater penitance

in the ecosystem and limited / no treatment options. The outbreaks of Multi-Drug Resistant (MDR) strains of *Salmonella enterica* serovar typhimurium in the Indian subcontinent, Southeast Asia, and Africa showed approximately 16 million cases and 60,000 deaths each year [4]. These infections which were earlier contained within hospitals, have now higher penetration even at community level [5]. *Salmonella* is also associated with reactive arthritis having global population expressivity in a range of 6 to 30%, out of which 0.2%–7.3% cases were of joint inflammation alone. Incubation period of reactive arthritis is ambiguous spanning a time period of 2-4 weeks after the onset of enteric infection [6]. Reactive arthritis is also reported to be associated with other food borne illness like *Campylobacter* and *Shigella* with reported infection rate of 1 and 4% in adults respectively [7]. Such findings implied that such infections are burdening the economic

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Received: September 30, 2015; **Accepted:** October 13, 2015; **Published:** October 16, 2015

Citation: Tanwar A, Thakur P, Chawla R, Jaiswal S, Chakotiya AS, et al. (2015) Targeting Antibiotic Resistant *Salmonella enterica*: Bio-matrix Based Selection and Bioactivity Prediction of Potential Nutraceuticals. *Biochem Anal Biochem* 4: 217. doi:10.4172/2161-1009.1000217

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setup of healthcare management attributed towards a longer duration of treatment with expensive antibiotics. Resistance in multidrug resistant pathogens is accredited to chromosomal mutations and selective pressure of several synthetic drugs used for the treatment [8]. Also, the resistance profile of *Salmonella enterica* serovar typhimurium indicates a shift from multidrug resistance to extensive drug resistance with resistance against tetracycline, streptomycin, sulfamethoxazole, ampicillin and ceftriaxone [9]. Emergence of strains resistant to ciprofloxacin further broadened its risk spectra. The mitigation of such risk at early stages is necessary so as to cease the consequent cascade of its use with biothreat intent. New therapeutic modalities with multi-targeted mode of action are needed to be investigated. The holistic mode of physiological action of natural plant products with reduced or nil adverse drug reactions might serve as the probable candidate(s) to be explored [10].

The present study utilized *in silico* bioprospection herbal informatics tool to filter the potential herbals targeted against virulence factors of MDR *Salmonella enterica* serovar typhimurium. It included web based classical data search, matrix linked data mining followed by fuzzy logic based optimization/ validation to identify potent herbals with probable therapeutic efficacy [11]. Furthermore, the selected herbals were screened for their biochemical activity at *in silico* level using 'Mol inspiration', a cheminformatics tool [12]. This study hence also illustrated the active leads for ascertaining desired biological activity, which further warrants antimicrobial efficacy testing at both *in vitro* and *in vivo* levels.

Methodology

Classical literature surge model

Antibiotic resistant *Salmonella enterica* serovar typhimurium was selected as the target pathogen. A classical literature surge model was utilized and ascertained Enterochelin/enterobactin (ENT) Inhibition, Type III secretory system (TSSIII) Inhibition, Lipopolysaccharides (LPS) Inhibition, Superoxide dismutase (SOD) Inhibition and Symptomatic relief provision as virulence factors [13]. Similarly, the database set of herbals was selected with attributable factors as a) Ethnopharmacological importance of plant; b) Relevance of Herb in traditional medicine; c) Availability factor or cultural acceptability in localized regions; d) Any vedic literature supporting its use; e) Investigations/ prior experience on potential of the herb; f) Indirect indications, if any.

Relevance factor linked binary matrix analysis

PubMed was used as the assigned search engine for keyword hits analysis. A combination keyword converging 'anti-microbial activity and virulence factor' was entered in the query search box of PubMed. Observation based analysis of first 20 hits was done for linking the relevance of each virulence factor with its direct significance in triggering the disease [14]. Percentage relevance of each virulence factor was evaluated using the following formula;

$$\%(\text{Relevance})_{\text{avg}} = \frac{(\text{No. of relevant hits based on observational analysis})}{\text{Total No. of Hits screened}} \times 100$$

The scrutinization of primary database set of NPPs was done with respect to presence or absence of a given bioactivity parameter in the NPP, as reported in either traditional databases or PubMed search engine.

Relevance factor linked weightage matrix analysis

On the basis of average percentage relevance, each bioactivity

parameter was assigned with a weightage score. Bioactivity parameter having maximum percentage relevance was assigned with a score of 05 and other succeeding parameters were provided with relative weightage scores based on unitary method evaluation. Evaluation of overall weightage of plants having a binary score >3 was done by multiplying their binary score with weightage score of existing bioactivity parameter. This step definitely out-ruled the possibility of any 'uncertainty factor', thereby reducing investigator's biasness. Plants with scores ≥ 3 from previous step were only utilized to identify potent leads [15].

Fuzzy set membership analysis and optimization

The following mathematical relationship was used to ascertain relative relevance within an identified set of herbals;

$$\mu S = \frac{(S - \text{Min } S)}{(\text{Max } S - \text{Min } S)}$$

Where, μS represents the desirability values of selected NPPs of the fuzzy set S. Min(S) and Max(S) are minimum and maximum scores, respectively, in the fuzzy set S [16]. The estimated μS were converted into a leveled score by using a scaled magnitude as optimization of identified potential set of NPPs.

In silico biochemical and molecular activity prediction using 'Mol Inspiration'

Preparation of ligand dataset

The 2D structures and the SMILES (Simplified Molecular-Input Line-Entry System) notation of predominant phyto-constituents of scrutinized herbals (~ Fuzzy Set Score of 1) were obtained from Pubchem [17].

Biological activity prediction

Canonical SMILES of each of the selected biologically active phyto-constituent was considered as the test set. Based on the analysis of large training set consisting of tens of thousands of the known biologically active compounds, computer program PASS analyzed the presence or absence of specific substructures in the test set in relation to the training set. Each substructure fragment contributed towards a bioactivity score for each listed activity i.e., GPCR Ligand, Ion Channel modulator, Kinase inhibitor, Nuclear receptor ligand and Protease inhibitor. This provided a total molecule activity score (a number, typically between -3 and 3). Molecules with the highest activity score had the highest probability to be active [12].

Results

Classical literature surge model

Classical Bioprospection was done utilizing Vedic literature, ethnopharmacological databases, PubMed and direct/indirect scientific evidences as the foundation for rationale based selection of herbals targeting MDR *S. enterica*. Also, pathophysiology of MDR *S. enterica* was reviewed so as to select the crucial 05 virulence factors as drug targets (Bioactivity parameters). These bioactivity parameters were selected on the basis of certain important characteristics including a) category of microorganism as lethal, sub-lethal, incapacitating agent; b) unavailability of a treatment regime/vaccine; c) re-emerging virulent forms from past; d) intended use as a bioweapon. Similarly, classical bioprospection of 50 herbals was done on the basis of their direct significance in a) symptomatic relief provision; b) cell wall synthesis inhibition; c) bacterial enzyme inhibition; and/or d) antibiotic resistance modification.

Relevance factor linked binary matrix analysis

On the basis of keyword hits scoring matrix, average percentage relevance was ascertained for each virulence factor of *Salmonella enterica* subvar typhimurium. Rationale for selection of each of these parameters is elucidated in Table 1. Highest percentage relevance was obtained for Lipopolysaccharide inhibition (~ 65%), followed by other parameters like Symptomatic relief provision, Type III secretory system (TSSIII) inhibition, Superoxide dismutase (SOD) inhibition and Enterochelin/enterobactin inhibition. Consequently weightage was given to selected parameters in the range of 0.05-5, based on statistical unitary approach, with highest weightage i.e. 5, given to Lipopolysaccharide inhibition, followed by other parameters in decreasing order, as explicated in Table 2. The binary matrix analysis of presence / absence of these virulence factors in 50 herbals revealed that 28 herbal plants showed score ≥ 3 i.e., the median cut off value (Table 3).

Weightage matrix based analysis and optimization

The weightage score matrix analysis of 28 scrutinized plants revealed that 10 plants showed highest weightage score ≥ 14.98 ,

thereby indicating their probable therapeutic utility against one or more of the targeted virulence factors. The final selection included *Abrus precatorius*, *Azadirachta indica*, *Camellia sinensis*, *Holarrhena antidysenterica*, *Andrographis paniculata*, *Adhatoda vasica*, *Euphorbia hirta*, *Ocimum sanctum*, *Terminalia arjuna* and *Terminalia bellerica* with an optimized fuzzy score of 1.0 (Table 4).

In silico biochemical activity prediction using ‘mol inspiration’

The bioactivity scores of the 10 scrutinized NPPs revealed that conessine (*Holarrhena antidysenterica*) was found to be highly bioactive (>0.5) towards GPCR ligands, whereas andrographolide (*Andrographis paniculata*), amyryn (*Euphorbia hirta*) and arjunolic acid (*Terminalia arjuna*) were found to be highly bioactive (>0.5) towards both Nuclear Receptor ligands and protease. None of the phyto-ligands were found to be exhibiting ion channel modulation and kinase inhibition. Abrin (*Abrus precatorius*) and Epicatechin gallate (*Camellia sinensis*) exhibited moderate bioactivity ($0.1 \leq$ Bioactivity Score ≤ 0.45) with respect to GPCR Ligand, Nuclear Receptor Ligand and Protease. Azadirachtin (*Azadirachta indica*), Vasicinolone

S.No.	Bioactivity parameter	Rationale for selection (Based on Classical Approach)
1.	Enterochelin/enterobactin(ENT) Inhibition [23]	<ul style="list-style-type: none"> Enterochelin is a cyclic polyester consisting of three residues of 2,3-dihydroxy-N-benzoylserine. Enterobactin, a physiologically active iron sequestering agent, is excreted into the medium by <i>S. typhimurium</i> under low iron conditions and is indispensable for growth. Enterochelin regulates the capacity of <i>S. typhimurium</i> to grow both <i>in vivo</i> and <i>in vitro</i>. Crude extracts of several plants like <i>Allium sativum</i>, <i>Acacia catechu</i>, <i>A. nilotica</i> etc have been found to be bacteriostatic against multidrug resistant (MDR) strains of <i>S. typhimurium</i>.
2.	Type III secretory system (TSSIII) Inhibition (<i>Injectisome</i> or <i>Injectosome</i>) [24]	<ul style="list-style-type: none"> Contains proteins that form a channel in the inner and outer bacterial membranes, as well as an extracellular needle that is used for transporting and injecting effector proteins into a host cell. <i>S. typhimurium</i> stimulates innate responses by delivering through this system, the bacterial effector proteins SopE, SopE2, and SopB & induces intestinal inflammation as well as other intestinal inflammatory pathologies. Phenolic compounds from medicinal herbs and dietary plants include phenolic acids, flavonoids, tannins, coumarins, lignans such as <i>Borago officinalis</i>, <i>Embelis ribes</i>, <i>Holarrhena antidysenterica</i>, <i>Thymus vulgaris</i> etc. that exhibited significant effects on type III secretory system.
3.	Lipopolysaccharide Inhibition (LPS) [25]	<ul style="list-style-type: none"> LPS, key component of the cell wall and is required for the cellular integrity. Toxicity is due to an outer membrane consisting largely of lipo-polysaccharides (LPS) which protect the bacteria from the environment. It is made up of an O-antigen (responsible for the host immune response), and lipid A (made up of two phosphorylated glucosamine which are attached to fatty acids. Phosphorylation of this leads to the toxicity, which connects it to the outer membrane. Several plant extracts have exhibited synergistic activity like <i>Zingiber officinalis</i>, <i>Semecarpus anacardium</i>, and <i>Terminalia bellerica</i> against gram negative microorganisms and inhibits inflammation.
4.	Superoxide dismutase (SOD) Inhibition [26]	<ul style="list-style-type: none"> Enzymes that catalyze the dismutation of superoxide (O_2^-) into oxygen and hydrogen peroxide. Human WBC's generate superoxide and other reactive oxygen species to kill bacteria. During infection, some bacteria therefore produce superoxide dismutase (<i>Specially sodA and sodB</i>) to protect themselves from being killed, which might be helpful for the survival of strain by acting against the phagocytic mechanism of the host. Plants extracts that have shown synergistic effects include <i>Terminalia bellerica</i> + <i>Zingiber officinalis</i> + <i>Embelia ribes</i> to inhibit the SOD antioxidant activity of <i>S. typhimurium</i>.
5.	Symptomatic relief [27]	<ul style="list-style-type: none"> <i>S. typhimurium</i> is known to cause bacteremia, with or without gastrointestinal involvement; typhoid or enteric fever; localized infections (e.g. bones, joints, and meninges) One of the possible disease management strategies is to alleviate the symptoms by using herbals like <i>Vitis vinifera</i>, <i>Piper longum</i>, <i>Allium sativum</i> etc. Active ingredient such as alkaloids, flavones, glycosides, etc of medicinal herbals have been known to show such symptomatic relief providing effects.

Table 1: Rationale for selection of the bioactivity parameters for Bioprospection study.

S.No.	Bioactivity parameter	Total No. of hits screened	Hits relevance (N=20)	Percentage (%) relevance	Relative weightage assigned
1.	Lipopolysaccharides inhibition (LPS)	190	13	65%	5
2.	Symptomatic relief	33	9	45%	3.46
3.	Type III secretory system(TSSIII) inhibition	43	7	35%	2.69
4.	Superoxide dismutase (SOD) inhibition	50	6	30%	2.30
5.	Enterochelin/enterobactin inhibition	32	4	20%	1.53

Table 2: Classical literature surge of virulence factors, showcasing relative percentage relevance.

S.No.	Plants	Plants code	Ethnopharmacological Importance	Traditional medicine	Availability	Indirect indication	Active ingredients and chemical constituents
1	<i>Abrus precatorius</i> (Rati) [28]	Ap	Abortifacient, anodyne, aphrodisiac, antimicrobial, diuretic, emetic, expectorant, febrifuge, sedative	Treatment of nervous systems, diarrhea, dysentery and possesses antihelminthic properties	Ubiquitous in India, Belize, Caribbean Islands, Hawaii, Polynesia and parts of the United States	Chloroform-methanol extract of <i>Abrus precatorius</i> seeds shows anti-diabetic effect. It is very helpful in lowering the level of blood sugar	Alkaloids 1%, abrin, abraline, choline, trigonelline, gallic acids, precatorine, abricin, abridin, abrectorin and several amino acids
2	<i>Aegle marmelos</i> (Bel) [29]	Am	Improves appetite and digestion, cure for dysentery and dyspepsia, fever and malaria Aromatic, astringent, cooling, febrifuge nature and also acts as tonic for heart and brain	Used for constipation, dysentery and diarrhea	South-east Asia	Shows hypoglycaemic activities. It also shows significant elevation in glutathione and Vitamin C	Tannins 5%, Mucilage 10% & Mucilage 15%, Main chemical components are marmelosin, alloimperatorin, marmelide, tannic acid, marmin, umbelliferone, isoimperatorin, isopimpinellin, skimmion, marmesin, marmesinin, fatty acids, and beta-sitosterol
3	<i>Acorus calamus</i> (vacha) [30]	Ac	Nauseant, stomachic, anthelmintic, stimulants, emetic, expectorant, carminative, antispasmodic and nerve sedative.	Useful in flatulence, colic, dyspepsia, dysentery, stomach problems cough, bronchitis, inflammations	Ubiquitous in India and other country.	Methanolic extract of rhizomes possess antimicrobial activity against bacteria, fungi and yeast	-
4	<i>Andrographis paniculata</i> (Kalmegh) [31]	Adp	Useful in diarrhoea, dysentery, enteritis, fever, cough, sore throat, bronchitis, hypertension, menstrual and post-partum hematometra	Anti-biotic, anti-viral, anti-parasitic and immune system stimulant used in viral hepatitis, children's bowel complaints, gastric acidity, liver congestion and flatulence	Cultivated throughout India, Southern and South-eastern Asia	Extract possesses antioxidant and anti-inflammatory properties.	Andrographolide 5% -10%. Main chemical components are diterpenoid lactones, paniculides, farnesols, flavonoids, andrographolide, andrographinin, neoandrographolide and isoandrographolide
5	<i>Azadirachta indica</i> (Neem) [32]	Adi	Anti-septic, anti-inflammatory, anti-bacterial, anti-hyperglycemic and insecticidal in nature. Useful in vomiting, dyspepsia, intestinal worms and hepatopathy	Act as vermifuge, insecticide, astringent, tonic and antiseptic	Evergreen and grows throughout India	Head Lice treatment and Measles symptoms alleviation	Bitters 2%, Bitters 3% & Bitters 5%, azadirachtin, azadirachtol, azadirachnol, desacetynimbinene, nimbandiol, nimbolide, quercetin, beta-sitosterol, n-hexacosanol, nimbiol and nimocin
6	<i>Adhatoda vasica</i> (Adosa) [33]	Av	Sedative, expectorant, antispasmodic and anti-helminthic. It is a bronchial antiseptic, bronchodilator and expectorant	Treating cold, cough, whooping cough, chronic bronchitis and asthma. Used in diarrhea and dysentery	Grows in plains & in lower Himalayan ranges upto 1000 m above sea level.	Potent antitussive effect	Vasicine 1.0%, Alkaloids 1%, 2'-hydroxy -4-glucosyloxychalcone, vasicol, adhatodine, vasicinone, vasicinol, arachidic, cerotic, behenic, lignoceric, linoleic and oleic acids
7	<i>Berberis aristata</i> (Daruhaldi) [34]	Ba	Anti-bacterial, anti-inflammatory, astringent, alternative, antipyretic, antiperiodic, anti-septic, anti-cancer	Useful in eye diseases, hemorrhoids, amenorrhoea, leucorrhoea, piles, sores, peptic ulcers, dysentery, heartburn, indigestion, hepatitis, intermittent fever, and chronic ophthalmia	Himalayan region, distributed from Kashmir to Uttarakhand	Root bark is anticoagulant and hypotensive in nature. It is also used to treat infections, eczema, psoriasis, and vaginitis	Kerachine, Berberine, oxycanthine etc
8	<i>Camellia sinensis</i> (Green tea) [35]	Cs	Antibacterial, antiseptic, antioxidant and detoxifying properties. Helpful in curing arthritis and asthma.	It enhances the liver functioning and immune system. Helpful in mental disorders, skin disorders and cardiovascular diseases	Green tea originated in China More widespread in the West	Leaves increase the body resistance against biological, physical and chemical stressors. It is known as a good adaptogen	Polyphenols 50%, 60%, 70%, caffeine, catechins, epigallocatechin, epigallocatechin gallate (EGCG), malic acid, oxalic acid, theophylline, theobromine, xanthine, inositol, kaempferol and quercetin
8	<i>Chamomile spp.</i> (Babun phool) [36]	Cms	Sedative, anodyne, antibacterial, stomachic.	Used as antimicrobial, antihistamine, anti-anxiety, diuretic	Southern Europe, Asia, North America	Chamomile is frequently added to skin cosmetics to serve as an emollient	Tannins, flavonoids resins etc
9.	<i>Euphorbia hirta</i> (Dudhi) [37]	Eh	Bronchitic, asthma and laryngeal spasm anodyne, antipruritic, carminative, depurative, diuretic, febrifuge, galactogogue	Used to treat intestinal amoebic dysentery, enteritis and skin conditions	Waste places and cultivated fields in lowland Japan, Nepal	Shown to kill various types of pathogenic bacteria, <i>Helicobacter pylori</i> and <i>Plasmodium</i>	-

10	<i>Ficus religiosa</i> (Peepal) [38]	Fr	Useful in inflammations and glandular swellings of neck. Used as astringent in leucorrhoea	Root, bark is aphrodisiac and also good for lumbago	Cultivated in south-west China and Indochina	-	-
11	<i>Hemidesmus indicus</i> (Anantmoola) [39]	Hi	Astringent, anti-inflammatory properties	Useful in treatment of skin diseases, wounds, psoriasis and syphilis, inflammations, hepatopathy and neuropathy.	Root extract shows potent anti-enterobacterial activity (<i>S. flexneri</i>)	-	Saponins 5%, 7.5% & 10%, sarsaponin, smilacin, p-methoxy salicylic aldehyde, beta-sitosterol, sarsapogenin, smilgenin, sitosterol, stigmasterol fatty acids and tannins
12.	<i>Holarrhena antidysenterica</i> (Indrajava) [40]	Ha	Astringents, antidysentric, stomachic, febrifungal and tonic properties	Useful in treatment of piles, skin diseases and biliousness. Herb for amoebic dysentery and other gastric disorders	Grows wild in mountains like Himalayas	Useful in Rheumatoid Arthritis & Osteoarthritis. Ethanolic extract showed antiprotozoan effect against <i>Trypanosoma evani</i>	Alkaloids, Conamine, kurchine, halorrhinene, conkurchine etc
13	<i>Lawsonia inermis</i> (Mehandi) [41]	Li	Useful in cephalgia, burning sensation, insomnia and fever	Protect against many surface fungi and bacteria and has been used for its cooling and astringent properties	Northern Africa, Western and Southern Asia	Ethanolic extract shows significant wound healing property	Tannins 5% & Tannins 10 %, lawsone, esculetin, fraxetin, isoplumbagin, scopoletin, betulin, betulinic acid, hennadiol, lupeol, lacoumarin, quinone and naphthaquinone
14	<i>Nelumbo nucifera</i> (Lotus) [42]	Nn	Useful in vomiting, dysentery, cholera, diarrhea, ringworm affection and dyspepsia, fever, intermittent fever, cough, burning sensation, dysuria and hyperdypsia	The rhizomes or leaves are used with other herbs to treat sunstroke, fever, diarrhoea, dysentery, dizziness and vomiting of blood. The whole plant is used as an antidote to mushroom poisoning	Tropical Asia Queensland, Australia India	Hydro alcoholic extract of seeds is a potent antioxidant. It exhibits strong free radical scavenging activity	Polysaccharides 2.5%-5% & Saponin 5%, nelumbine, nuciferine, dehydronuciferine, β -sitosterol, asparagine, nelumboside, lotusine, neferine, palmitic acid, nicotinic acid, glucose and amino acids
15	<i>Ocimum sanctum</i> (Tulsi) [43]	Os	Diaphoretic, anti periodic, stimulating, expectorant and anti-catarhal. Used in malaria, bronchitis and gastric disorders	Used as skin ointments and promoted as a treatment for acne	Eastern-World India and Nepal	Extracts have shown some antibacterial activity against <i>E. coli</i> , <i>S. aureus</i> and <i>P. aeruginosa</i> . Mitigation effects of radiation exposure.	Tannins 2%,5%,10%, Urosolic Acid 1.5%, tannins, alkaloids and volatile oil
16.	<i>Piper longum</i> (Kali mirch) [44,45]	PI	Used to treat flatulence, gout, laryngitis, and paralysis, abdominal tumors and gastric ulcers.	Good for aromatic, stimulant, carminative, constipation, gonorrhoea, paralysis of the tongue, diarrhea, cholera & respiratory infections	-	Extract possesses significant immunomodulatory, anti-arthritic and anti-tumor activity	Piperine 3%, Rutin 4%- 6%, beta- caryophyllene piperylene, piperoleines
17.	<i>Syzygium cumini</i> (Jamun) [46]	Syc	Antidiabetic agent by decreasing kidney's catalase activity, Antihelminthic, Astringent	Useful in diabetes, diarrhoea and ringworm infection. Leaves and bark are used for controlling blood pressure and gingivitis	Bangladesh, India, Nepal, Sri Lanka, Indonesia	Bark extract possesses potent anti-inflammatory activity	Bitter 3%, Bitter 5% & Volatile Oil 1%, methylxanthoxylin, corilagin, ellagitanins, ellagic acid and gallic acid, jambosine, volatile oil, jambolin, quercetin, ferulic acid, veratrole, guajacol and caffeic acid
18.	<i>Terminalia arjuna</i> (Arjuna) [47]	Taj	Astringent, sweet, acrid, cooling, aphrodisiac, cardiotonic, urinary astringent, expectorant, alexiteric and is useful in fractures, ulcers, cirrhosis of the liver, hyperhidrosis, otalgia and hypertension	It improves cardiac muscle function and pumping action of the heart. Useful for asthma, bile duct disorders, scorpion stings, and poisonings	West Bengal and south and central India	Bark shows potent anti-anginal and cardio-protective activity	Arjunolic Acid 0.5%, Tannin 25%, tannins, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin and arjunic acid), flavonoids, gallic acid, ellagic acid and phytosterols
19.	<i>Terminalia bellerica</i> (Behada) [48]	Tb	It is astringent, tonic, expectorant and laxative	Useful in cough, bronchitis and pharyngitis. Used in dyspepsia, flatulence, dipsia, and vomiting	Ubiquitous in India Southeast Asia,	Extract reduces the levels of lipids in hypercholesterolemia models.	Tannins 40% & Tannins 60%, β -sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid

20.	<i>Thymus vulgaris</i> (Thyme) [49]	Tv	Anthelmintic, strongly antiseptic, antispasmodic, carminative, deodorant, diaphoretic, disinfectant, expectorant, sedative and tonic	Treatment of dry coughs, whooping cough, bronchitis, bronchial catarrh, asthma, laryngitis, indigestion, gastritis and diarrhoea	Indigenous to mediterranean regions and southern europe, but prospers almost anywhere in temperate climate	Extract shown antibacterial activity against the gram negative bacteria	Main chemical components are a-thujone, a-pinene, and camphene
21	<i>Vitis vinifera</i> (Angoor) [50]	Vv	Used for the treatment of cancer, cholera, smallpox, nausea, skin and eye infections as well as kidney and liver diseases	Leaves being used to stop bleeding, pain and inflammation	Central Europe south-western Asia	Used as anti-inflammatory and antibacterial agents	Phenolic compounds
22	<i>Allium satium</i> (Garlic) [51]	As	Antiseptic and antimicrobial activity	Use to prevent scurvy, because of its high vitamin C content	Asia, South Asia, Southeast Asia, Africa, Europe	Extract yields allicin, an antibiotic and antifungal compound	Vitamins, proteins, minerals, saponins, flavonoids.
23	<i>Zingiber officinalis</i> (Ginger) [52]	Zo	Clinically proven as prophylactic of nausea and vomiting associated with motion, sickness, sea sickness and pregnancy. Known for its gastrointestinal benefits and as an anti-inflammatory and carminative.	Used in dyspepsia, diarrhoea, colic, flatulence, vomiting, nausea, cough, cold, asthma	South east Asia and throughout India	Rhizome is a potent inhibitor of platelet activation and aggregation	Gingerols 5%, gingeole, zingerone, shogaol, zingiberene, cineol, borneol, phellandrene, citral, zingiberene, linalool, geraniol, chavicol, vanillyl alcohol, camphene and resin
24	<i>Acacia nilotica</i> [53]	An	Strongly astringent due to tannin algicidal activity	Useful in treatment of diarrhea, dysentery, fever, gallbladder, hemorrhage, hemorrhoids, leucorrhoea	Zanzibar, Pemba, and India; Arabia	Algicidal activity against <i>Chroococcus</i> , <i>Closterium</i> , <i>Coelastrum</i> , <i>Cosmarium</i>	Sulphoxides pentosan, saponin, tannin. Seeds contain crude protein 18.6%, ether extract 4.4%, fiber 10.1%, nitrogen-free extract 61.2%
25	<i>Withania somnifera</i> (Ashwa gandha) [54]	Ws	Used as tonic, abortifacient, astringent, deobstruent, nervine, aphrodisiac and sedative	Rheumatism, leprosy and arthritis	Dried regions of India, such as Punjab, Sindh, and Rajasthan. It is also found in Nepal	Inhibits the growth of human tumor cell line. It increases the levels of corticosterone in the adrenal glands of stress	Alkaloids 1%, Alkaloids 2%, Withanolides 1.5% & Withanolides 2%, glycosides, withanolides, withasomnine, hentriacontane, dulcitol, withaniol and withaferin
26	<i>Acacia catechu</i> [55]	Ac	Strong antioxidant, astringent, anti-inflammatory, anti-bacterial and anti-fungal in nature	Useful in stomach problems like diarrhea, dysentery, colitis and gastric cancer	Asia, China, India and the Indian Ocean area	Extract has significant antipyretic, anti-diarrhoeal, hypoglycaemic and hepatoprotective properties	Tannins 25%, Catechin 10%, catechuic acid, pyrocatechin, phloroglucin, protocatechuic acid, quercetin, gum and minerals
27	<i>Semecarpus anacardium</i> (Bhalltak) [56]	Sa	Useful in leucoderma, scaly skin, allergic, dermatitis, poisonous bites, leprosy, cough, asthma, and dyspepsia	Act as insecticides, antiseptic, termite repellents and herbicide	India	-	Anacardic acid 0.4%, Proteins
28	<i>Punica granatum</i> (Anar) [57]	Pg	Antioxidant, Anticarcinogenic and anti-inflammatory properties	Stomach carcinoma and syphilis treatment	Cultivated in India	Seed extract possess hypoglycaemic activity	Ellagic Acid 20%, Ellagic Acid 40% & Tannins 25%, punicalagin, ellagic acid, luteolin etc

Table 3: Herbal plants showing probable utility against *Salmonella enterica* serovar typhimurium infections.

S.No.	Herbal Plant	Herbal code	Binary score	Weightage score	Fuzzy score (µS)
1	<i>Andrographis paniculata</i>	Ap	5	14.98	1
2	<i>Azadirachta indica</i>	Ai	5	14.98	1
3	<i>Adhatoda vasica</i>	Av	5	14.98	1
4	<i>Euphorbia hirta</i>	Eh	5	14.98	1
5	<i>Ocimum sanctum</i>	Os	5	14.98	1
6	<i>Terminalia arjuna</i>	Ta	5	14.98	1
7	<i>Terminalia belerica</i>	Tb	5	14.98	1
8	<i>Abrus precatorius</i>	Ap	5	14.98	1
9	<i>Camellia sinensis</i>	Cs	5	14.98	1
10	<i>Holarrhena antidysenterica</i>	Ha	5	14.98	1
11	<i>Aegle marmelos</i>	Am	4	13.45	0.867
12	<i>Vitis vinifera</i>	Vvf	4	13.45	0.867
13	<i>Acacia catechu</i>	Ac	4	12.68	0.8
14	<i>Berberis aristata</i>	Ba	4	12.68	0.8
15	<i>Ficus religiosa</i>	Fr	4	12.68	0.8

16	<i>Punica granatum</i>	Pg	4	12.68	0.8
17	<i>Nelumbo nucifera</i>	Nn	4	12.68	0.8
18	<i>Rosmarinus officinalis</i>	Ro	4	12.68	0.8
19	<i>Syzygium cumini</i>	Syc	4	12.68	0.8
20	<i>Chamomile spp.</i>	Cms	4	12.68	0.8
21	<i>Zingiber officinale</i>	Zo	4	12.68	0.8
22	<i>Acacia nilotica</i>	An	4	12.68	0.8
23	<i>Hemidemus indicus</i>	Hi	4	12.68	0.8
24	<i>Withania somnifera</i>	Ws	4	12.68	0.8
25	<i>Acorus calamus</i>	Ac	4	12.68	0.8
26	<i>Semecarpus anacardium</i>	Sa	4	12.68	0.8
27	<i>Lawsonia inermis</i>	Li	4	12.68	0.8
28	<i>Thymus vulgaris</i>	Tv	4	9.98	0.567

Table 4: Fuzzy Set Membership Analysis for herbal plants screened on the basis of Binary and Weightage Matrix scores.

S.No	Herbal Plant	Predominant Phytoconstituent	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Inference
1	<i>Holarrhena antidysenterica</i>	Conessine	0.63	0.13	-0.32	0.25	0.51	GPCR Ligand and Protease inhibition activity
2	<i>Andrographis paniculata</i>	Andrographolide	0.32	0.17	-0.01	0.94	0.81	Nuclear Receptor Ligand and Protease inhibition activity
3	<i>Euphorbia hirta</i>	Amyrin	0.22	-0.05	-0.31	0.67	0.56	Nuclear Receptor Ligand and Protease inhibition activity
4	<i>Terminalia arjuna</i>	Arjunolic acid	0.20	-0.22	-0.38	0.80	0.63	Nuclear Receptor Ligand and Protease inhibition activity
5	<i>Camellia sinensis</i>	Epicatechin gallate	0.17	0.02	0.05	0.34	0.13	Moderate activity
6	<i>Abrus precatorius</i>	Abrin	0.45	0.44	-0.03	-0.36	0.27	Moderate activity
7	<i>Azadirachta indica</i>	Azadirachtin	-0.71	-1.51	-1.46	-0.67	-0.35	No Bioactivity
8	<i>Adhatoda vasica</i>	Vasicinolone	-0.25	-0.25	-0.33	-0.51	-0.87	No Bioactivity
9	<i>Ocimum sanctum</i>	Eugenol	-0.86	-0.36	-1.14	-0.78	-1.29	No Bioactivity
10	<i>Terminalia bellerica</i>	Chebulagic acid	-3.51	-4.13	-4.15	-4.00	-3.24	No Bioactivity

Table 5: *In Silico* bioactivity scores of selected natural plant products.

(*Adhatoda vasica*), Eugenol (*Ocimum sanctum*) and Chebulagic acid (*Terminalia bellerica*) were found to exhibit nil bioactivity with respect to all the bioactivity predictors (Table 5). Final categorized NPPs on the basis of matrix based selection and *in silico* biochemical analysis were *Holarrhena antidysenterica*, *Andrographis paniculata*, *Euphorbia hirta*, *Terminalia arjuna*, *Abrus precatorius* and *Camellia sinensis*.

Discussion

Antibiotics, the defense resort against the sturdy pathogens of commensal as well as nosocomial origin, are now losing the battle against multi-drug resistant re-emerging pathogens e.g., *Salmonella enterica* serovar typhimurium (diversified food borne pathogen) [18]. Such conflict has arisen due to the irrational usage of antibiotics, thereby transforming commensals into extensively drug resistant forms. Natural selection and sudden mutations might be conferring resistance in these pathogens [8]. The present day synthetic drugs are not competent enough to overcome the irreversible effects of such resistance patterns. Limitations of chemotherapeutic moieties i.e., systemic toxicity and adverse drug reactions, hence require to be out-ruled by instigating the search for newer antimicrobials of plant origin having holistic potential [1].

The present study utilizes an ethnopharmacological approach amalgamated with informatics for rationale based selection of herbals. Random search model approach was devised using PubMed as the search engine. 05 bioactivity parameters were selected on the basis of their direct/ indirect role in a) symptomatic relief provision, b) antibiotic resistance modification, c) bacterial enzyme modification, d) cell wall synthesis inhibition (Table 1). This bioprospection study was

found to be in consonance with a similar study of the evaluation of sleep wake cycle in healthy individuals conducted by Elizabeth S. Jenuwine et al. [19]. The importance of herbal informatics model can further be viewed from the fact that herbals have been used as the main reservoir for a variety of natural plant products having bio-protection abilities e.g., Taxol (anticancerous, *Taxus baccata*), Silymarin (radioprotector, *Silybum marianum*), Vincristine (anticancerous, *Rosmarinus officinalis*), Vinblastin (anticancerous, *Rosmarinus officinalis*) etc [20].

Binary coefficient matrix analysis, the first screening step of herbal informatics, was used to identify herbals on the basis of all or none principle, thereby eliminating the outliers which have scored less than the median cut off value i.e., >3. After the first screening step, 28 plants were filtered from a pool of 50 plants, thus reducing the total time of execution. Furthermore, weightage matrix based analysis was used to scrutinize the selection process in case of 02 or more herbals with identical binary score. Final decision of selection of herbals was based on fuzzy set membership analysis, so as to provide a universally acceptable optimized score [16].

The final categorized set of plants included *Abrus precatorius* (Rati), *Azadirachta indica* (Neem), *Camellia sinensis* (Green tea), *Holarrhena antidysenterica* (Indrajava), *Andrographis paniculata* (Kalmegh), *Adhatoda vasica* (Adosa), *Euphorbia hirta* (Dudhi), *Ocimum sanctum* (Tulsi), *Terminalia arjuna* (Arjuna) and *Terminalia bellerica* (Behada). All these above mentioned plants have been reported to contain a variety of secondary metabolites like conessine (alkaloid, *Holarrhena antidysenterica*); andrographolide (alkaloid, *Andrographis paniculata*) and epicatechin gallate (flavonoid, *Camellia sinensis*) etc [1,20].

Furthermore, the cheminformatics based biochemical activity prediction of predominant phytoconstituents of these NPPs gave an insight of their mechanistic mode of action. Phytoconstituents which were exhibiting bioactivity with respect to either GPCR or Nuclear receptor ligand (i.e., Conessine, Andrographolide, Amyrin, Arjunolic acid) might have a direct or indirect role in regulation of immune system activity and inflammation. Both G protein-coupled receptor signaling and Nuclear Receptor binding lead to mast cell degranulation which subsequently induces localized inflammation and bacterial antigen clearance [21]. Moreover secondary metabolites with bioactivity linked to protease inhibition (e.g., Conessine, Andrographolide, Amyrin, Arjunolic acid) is directly contemplating the antimicrobial activity of these phytoconstituents as protease is known to be a key enzyme of bacteria required for evasion of host immune defenses, nutrients acquisition for growth and proliferation and tissue necrosis [22]. These secondary metabolites of NPPs might therefore, be responsible for their holistic antibacterial action, which can further be tested and validated at *in vitro* and *in vivo* levels.

Conclusion

The study has provided 06 NPPs i.e., *Holarrhena antidysenterica*, *Andrographis paniculata*, *Euphorbia hirta*, *Terminalia arjuna*, *Abrus precatorius* and *Camellia sinensis* with significant therapeutic potential that need to be explored at *in vitro* and pre-clinical level to manage MDR *Salmonella enterica* serovar typhimurium and other related infections.

Acknowledgements

The authors are grateful to Director, INMAS and Vice Chancellor, Jamia Hamdard for provision of research facilities and support. The present study was conducted under the Project number INM-318 of 'Samarthya' Programme of DRDO.

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Citation: Tanwar A, Thakur P, Chawla R, Jaiswal S, Chakotiya AS, et al. (2015) Targeting Antibiotic Resistant *Salmonella enterica*: Bio-matrix Based Selection and Bioactivity Prediction of Potential Nutraceuticals. *Biochem Anal Biochem* 4: 217. doi:[10.4172/2161-1009.1000217](https://doi.org/10.4172/2161-1009.1000217)

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