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***IN-SILICO* HERBAL INFORMATIC APPROACH FOR IDENTIFICATION  
OF MEDICINAL PLANTS TARGETING *STAPHYLOCOCCUS AUREUS***

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**ABSTRACT**

*Staphylococcus aureus* is becoming a more vulnerable pathogen common in the community and hospitals, resulting in more cases of illness and deaths. Irrational antibiotic use has been linked to *Staphylococcus aureus* infection, which has worsened the already concerning situation and led to endemic and epidemic diseases worldwide. The need to develop traditional herbal medicine into a sophisticated Ayurvedic Medicinal System (AMS) strategy is driven by the current threat of antibiotics and their resistance to public health. The current study uses herbal informatics as a comprehensive approach in identifying the effective herbal remedies to counter the threat posed by *Staphylococcus aureus*. Six plants were optimized and may be further validated at the preclinical level after being tested against the virulence factors of the bacterium using a systematic bioprospecting approach. The leads/drug-like herbals identified by the herbal informatics model could be helpful for *in vitro* and *in vivo* research to create therapeutic herbal medicines.

**Keywords:** Bioprospection; *Staphylococcus aureus*; Traditional medicine; Ethnopharmacology

**INTRODUCTION**

A significant human and animal opportunistic pathogen called *Staphylococcus aureus* causes nosocomial and community-associated infections with

substantial morbidity and mortality rates [1].

It is the primary cause of several illnesses including pneumonia, bacteremia, osteoarticular infections, skin, soft tissue, surgical site, and catheter infections [2].

According to the estimates, the global infection rate for *Staphylococcus aureus* ranges from 25% to 35% [3]. Several studies on Methicillin-resistant *Staphylococcus aureus* (MRSA) highlight the harmful effects of resistant bacterial infections on society and healthcare [4], at an infection rate ranging up to 22.6% in India [5]. Antibiotic resistance is a widespread issue that is more severe in underdeveloped nations. Bacterial resistance dramatically increases the duration of therapy and the risk of side effects, both of which drive up the cost of care [6]. Antimicrobial drug use has a crucial global impact on establishing drug-resistant strains.

Despite the availability of several antimicrobial medicines and the development of novel antibiotics, the phenomenon of antibiotic resistance remains one of the leading causes of death globally [7]. Complementary and alternative medicine therapies (CAMTs), which are increasingly popular worldwide, are divided into drug-based CAMTs and nondrug-based CAMTs [8].

A comprehensive strategy is used by herbal medicines to treat *Staphylococcus aureus*. The current research focuses on the justification for using a herbal informatics approach to bioprospection and identifying, examining, and evaluating the Alternative Medicine System (AMS) based on its

ethnopharmacological qualities as described in Vedic literature.

## METHODOLOGY

### Classic Literature Surge model

Using a traditional bioprospection technique and literature surge, bioactivity parameters were chosen considering the sympathetic aspects of infection produced by *Staphylococcus aureus*.

### Relevance factor binary matrix analysis

Each virulence parameter and its relevance factor/net weightage were calculated using the following equation after linking the keyword search *Staphylococcus aureus* infections and virulence factor inhibition with observation-based analysis of the first 20 hits [9].

$$\text{Percentage relevance} = \frac{\text{Relevant hits}}{20} \times 100$$

### Bioprospection method for herbals identification

The following variables are investigated using the traditional bioprospecting method based on a literature review to come to a logical conclusion that leads to the selection of plants. It consists of various factors including

- Ethnopharmacological significance
- Usage of herbs in indigenous medicine
- Cultural acceptability or the availability factor in specific locales
- Any Vedic writings that justify its application

- Research and past experience on the herb's potential were considered [10].

Accordingly, 20 herbals including *Aloe vera* (L.) Burm.f, *Glycyrrhiza glabra* L., *Rheum palmatum* L., *Myrica nagi* Thunb., *Morus nigra* L., *Thymus vulgaris* L., *Curcuma longa* L., *Oroxylum indicum* (L.) Kurz, *Matricaria chamomilla* L., *Syzygium aromaticum* (L.) Merr & L. M. Perry, *Psidium guajava* L., *Sophora flavescens* Aiton, *Cyperus rotundus* L., *Punica granatum* L., *Capsicum annuum* L., *Rhodomyrtus tomentosa* (Aiton) Hassk., *Tinospora cordifolia* (Willd.) Miers., *Humulus lupulus* L., *Camellia sinensis* (L.) Kuntze., *Allium sativum* L., were selected and were tabulated in **Table 1**.

#### **Weightage matrix-based scrutiny**

Assessment of the overall weightage of plants (scores  $\geq 3$  in the previous step) was validated by multiplying their binary score with the weightage (as obtained in the above step). This step further augments the 'uncertainty factor' essential for the statistically significant outcome to identify the potential drug-like herbals to cross-validate at the next level of fuzzy set optimization.

#### **Fuzzy set optimization for the decision matrix**

The below mathematical relationship was used to determine the relative importance of a set of identified herbals [11].

$$\mu S = \frac{[(S) - \min(S)]}{\max(S) - \min(S)}$$

where  $\mu S$  is the Fuzzy value; S is the Weightage matrix score

Table 1: List of Preferred Herbals and their therapeutic importance

S. No.	Medicinal plants	Pharmacological activities	Occurrence	Traditional uses	Major phytoconstituents	Reference
1.	<i>Aloe vera</i>	Wound healing, anti-inflammatory, antitumor, antidiabetic, antibacterial	India, Mexico, South America, Central America	Constipation, Worm infestation, laxative, Haemorrhoid treatment	Aloe emodin, chrysophanol, Aloin, Barbaloin, Emodin	[12]
2.	<i>Glycyrrhiza glabra</i>	Antiviral, antibacterial, antidiabetic, antitussive, anticoagulant	India, Iraq, Uzbekistan, Pakistan, China, Turkey, Turkmenistan, Azerbaijan	Cathartic for animals, Cure cough and sore throat	Glycyrrhetic acid, Glabrene, Gabridin	[13]
3.	<i>Rheum palmatum</i>	Antibacterial, antifungal, antidiabetic, antiulcer	Northwest China	To treat the purging effect and in fever	Rhein, Chrysophanol, Emodin	[14]
4.	<i>Myrica nagi</i>	Antimicrobial, anxiolytic, anthelmintic, anti-inflammatory, antioxidant	China, Japan	Reducing inflammations, asthma, bronchitis, cough, and urinary discharges	Myricetin, myricanone, gallic acid, ethyl $\beta$ -D glucopyranoside	[15]
5.	<i>Morus nigra</i>	Anti-inflammatory, antibacterial, antidiabetic, antiobesity, anti melanogenic	Asia, Germany, Austria, Switzerland	Antitussive	Chalcone	[16]
6.	<i>Thymus vulgaris</i>	Antioxidant, anti-inflammatory, antimicrobial, insecticidal	Europe, Italy	Sciatica, acne, dermatitis and insect bites	Carvacrol	[17]
7.	<i>Curcuma longa</i>	Antibacterial, anticancer, antidiabetic, antioxidant	India	Body pain, digestive disorders, rheumatoid arthritis	Curcumin	[18]
8.	<i>Oroxylum indicum</i>	Anti-inflammatory, antihepatotoxic, anthelmintic, antimicrobial	Bhutan, China, India	Snakebite	Baicalein	[19]
9.	<i>Matricaria chamomilla</i>	Analgesic, anticancer, anti-inflammatory, antimicrobial	China, Australia, India	Diabetes, nervous disorders, painful menstruation	Farnesol	[20]
10.	<i>Syzygium aromaticum</i>	Antimicrobial, antioxidant, analgesic, antifungal, anti-inflammatory	Indonesia, Sri Lanka, India, Tanzania, Malaysia, Madagascar	Toothache	Eugenol acetate	[21]
11.	<i>Psidium guajava</i>	Antibacterial, anticancer,	Caribbean islands,	Febrifuge, antispasmodic, rheumatism	Chalcone	

		hypoglycaemic, antioxidant, antidiarrheal	America, India.			[22]
12.	<i>Sophora flavescens</i>	Antibacterial, antifungal, antiviral, antitumor	India, China	Antipyretic, analgesic, anthelmintic, stomachic	Quercetin	[23]
13.	<i>Cyperus rotundus</i>	Analgesic, antibacterial, diuretics, antioxidant, analgesic	Africa, Central Europe, Asia	Gastrointestinal spasms, stomach disorders, nausea, vomiting	$\alpha$ -cyperone	[24]
14.	<i>Punica granatum</i>	Antibacterial, antidiabetic anticancer, wound healing, anti-inflammatory	India, America, Spain	Diarrhea and vaginal discharge	Punicalagin	[25]
15.	<i>Capsicum annum</i>	Anti-inflammatory, anticancer, antiviral, antioxidant	Caribbean islands, America, India	Circulatory stimulant.	Capsaicin	[26]
16.	<i>Rhodomyrtus tomentosa</i>	Antibacterial, antifungal, antiulcer, anti-inflammatory	Asia, India, Malaysia	Blood enricher, rheumatism, treating uterine bleeding	Rhodomyrtone	[27]
17.	<i>Tinospora cordifolia</i>	Antimicrobial, antidiarrhoeal, anthelmintic, antiviral	India, Myanmar, Sri Lanka, China, Thailand, Philippines	Fever, jaundice, diarrhoea.	Palmatine Furanolactone	[28]
18.	<i>Humulus lupulus</i>	Antibacterial, antimalarial, anticancer, sedative	Denmark, Norway, Sweden, Finland	Leprosy, toothache, fever, gastric problems	Xanthohumol	[29]
19.	<i>Camellia sinensis</i>	Wound healing, antiviral anticancer, antioxidant, Hypocholesterolaemia	Southern China, India	Headaches, asthma, diabetes, low blood pressure	Epigallocatechin gallate, Epigallocatechin	[30]
20.	<i>Allium sativum</i>	Antioxidant, antimicrobial, Anticancer, anti-inflammatory, antidiabetic, antithrombotic	Iran	Food poisoning, parasitic infections, tumors, lower blood pressure	Allin, Allicin, 5- Hydroxymethyl furfural	[31]

Table 2: Binary Score Matrix of Herbs based on Bioactivity

S. No.	Plants	Agr quorum sensing (Weightage factor- 3.95)	Bio-film formation (Weightage factor- 5.00)	$\alpha$ -hemolysin (Weightage factor- 3.16)	Sortase-A (Weightage factor- 3.68)	Staphyloxanthin (Weightage factor- 3.16)	Binary score	Weightage score
1.	<i>Aloe vera</i>	1	1	0	0	0	2	8.95
2.	<i>Glycyrrhiza glabra</i>	1	1	1	0	0	3	12.11
3.	<i>Rheum palmatum</i>	1	1	0	0	0	2	8.95
4.	<i>Myrica nagi</i>	0	1	1	1	1	4	15.00
5.	<i>Piper nigrum</i>	1	1	1	1	0	4	15.79
6.	<i>Thymus vulgaris</i>	1	1	0	0	0	2	8.95
7.	<i>Curcuma longa</i>	0	1	1	1	0	3	11.84
8.	<i>Oroxylum indicum</i>	1	1	1	0	0	3	12.11
9.	<i>Matricaria chamomilla</i>	0	0	0	0	1	1	3.16
10.	<i>Syzygium aromaticum</i>	1	1	1	0	1	4	15.27
11.	<i>Psidium guajava</i>	0	1	0	1	0	2	8.68
12.	<i>Sophora flavescens</i>	0	1	1	1	0	3	11.84
13.	<i>Cyperus rotundus</i>	0	1	1	0	0	2	8.16
14.	<i>Punica granatum</i>	0	1	1	1	0	3	11.84
15.	<i>Capsicum annum</i>	0	1	1	0	0	2	8.16
16.	<i>Rhodomyrtus tomentosa</i>	0	1	0	0	1	2	8.16
17.	<i>Tinospora cordifolia</i>	0	0	0	1	0	1	3.68
18.	<i>Humulus lupulus</i>	0	1	0	0	1	2	8.16
19.	<i>Camellia sinensis</i>	0	1	1	0	0	2	8.16
20.	<i>Allium sativum</i>	0	1	0	0	0	1	5.00

Table 3: Fuzzy Score Analysis of Herbs

S. No.	Plants	Weightage score	$\mu^*$	Optimization score
1.	<i>Piper nigrum</i>	15.79	1	+++++
2.	<i>Syzygium aromaticum</i>	15.27	0.868	++++
3.	<i>Myrica nagi</i>	15.00	0.800	+++
4.	<i>Glycyrrhiza glabra</i>	12.11	0.068	-
5.	<i>Oroxylum indicum</i>	12.11	0.068	-
6.	<i>Curcuma longa</i>	11.84	0	-

+++++ denotes  $\mu^*=1$ ; ++++ denotes  $\mu^*=0.85-0.99$ ; +++ denotes  $\mu^*=0.750-0.85$

## RESULTS

### Bioactivity parameter analysis

The classical literature surge estimated with 5 bioactivity parameters and a database of 20 herbals paved the way for 8 NPPs (binary value  $\geq 3$ ), in which 3 herbals showed promising relevance towards 5 virulence descriptors.

### Relevance factor analysis

The percentage relevance factor for each of the 5 bioactivity parameters was estimated using a keywords hit scoring analysis. Biofilm formation was found to have the highest percentage of relevance (95%), followed by the Agr quorum sensing system, Sortase-A,  $\alpha$ -haemolysin, and Staphyloxanthin. Relevance factor linked binary-weightage matrix-based analysis and optimization

### Analysis and optimization using a binary weightage matrix linked to the relevance factor

In 20 herbals, the presence or absence of these virulence factors was analyzed using a binary matrix which is represented in **Table 2**. The results showed that 6 herbal plants had binary median cut-off scores of less than 3. The weightage score matrix analysis of 6 chosen plants showed that *Piper nigrum*, *Syzygium aromaticum*, and *Myrica nagi* showed a maximum weightage score of 15.79, 15.27 and 15.00 with an optimized fuzzy score of 1.0 which was represented in **Table 3**.

## DISCUSSION

Antibiotics' clinical usage was undoubtedly the most prominent medical breakthrough of the twentieth century [32]. Antibiotic resistance emerged concurrently with their development as life-saving treatments [33]. Over the last few decades, there has been a growing disparity between the need for novel antibiotics and their availability to patients. As a result, we are losing our ability to treat and prevent bacterial infections [34]. Natural product antibacterial research is the only option as the resistance pendulum swings back. The key to bacterial vulnerability is found in natural scaffolds.

On the other hand, the ethnopharmacological significance of several medicinal plants and their correct application as medicine is still being debated [7]. The present study logically explains conventional bioprospection, employing a comprehensive mathematical approach to produce unbiased results. This strategy involves identifying bioactivity parameters through a literature search, indexing their priority, and preparing a vast database of plants for scoring, decision matrix, and optimization of their final weightage [9].

The current study presented an *in-silico* strategy to target numerous bioactivities such as ag sensing, biofilm development, sortase-A,  $\alpha$ -Haemolysin, Staphyloxanthin, and others responsible for the evolution of multi-drug resistance. Using a binary matrix

approach based on the all or none principle to identify the herbal compound, the herbal compounds with scores below the median cutoff of three were eliminated. The binary scoring of plants for enduring the weightage matrix and the fuzzy set optimization was then cross-validated on 8 out of 20 plants, yielding a score that was overwhelmingly satisfactory for further validation of the examined lead at the molecular level.

Thus this study has revealed 06 medicinal plants i.e., *Piper nigrum*, *Syzygium aromaticum*, *Myrica nagi*, *Glycyrrhiza glabra*, *Oroxylum indicum*, and *Curcuma longa*, with a substantial therapeutic effect against *Staphylococcus aureus*. Further research can be done on these herbs to determine their therapeutic efficacy at both *in vitro* and *in vivo* levels.

#### Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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