

## ANTIBACTERIAL ACTIVITY AND MOLECULAR CHARACTERISTICS OF INDIAN OLIBANUM (*BOSWELLIA SERRATA*) PHYTOCHEMICALS: AN IN SILICO APPROACH

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**Abstract.** An unhealthy community is a reservoir for the global threat of Nosocomial infection. Rapidly escalating drug resistance and nosocomial infections resulting from the search for a novel drug is a tough challenge to upcoming researchers. Indian olibanum extract is held in high regard in the field of traditional medicines. To evaluate the antibacterial properties of *B. serrata* aqueous and hydroethanolic extract was taken with an in silico approach using Autodock vena tool. The nosocomial pathogens were detected from wound and skin samples in the Hospitals and from around Namakkal. Among the gram-negative nosocomial pathogen *Klebsiella oxytoca* and gram-positive *Staphylococcus aureus* were branded by microscopic and biochemical profiling. In addition, the susceptibility and resistance to antibiotics were explored for *K. oxytoca* and *S. aureus* in the case of tetracycline (21 mm and 28 mm), chloramphenicol (23 mm and 16 mm), and gentamycin (14 mm and 21 mm) respectively. The seven bioactive compounds were attained by GCMS. The inhibition zone of 18 mm at 60 µg deliberation for both the isolates viz *K. oxytoca* and *S. aureus*. In silico approach of phyto-bioactives with Beta-lactamase (AmpC) was investigated by Autodock vena tool. In silico Molecular docking approach examined the binding energy as -7.6 (kcal/mol) for Cholan-24-oic acid, 3,12-bis(acetyloxy) followed by Pyrene, hexadecahydro- -7.5 (kcal/mol), 5(1H)-Azulenone, 2,4,6,7,8,8a-hexahydro-3,8-dimethyl-4-(1-methylethylidene)-, (8S-cis)- -6.7 (kcal/mol). The conclusion of the finding is that phyto-bioactives of *B. serrata* also promote natural healing and antibacterial potential.

**Keywords:** bioactives, phyto-extracts, natural healing, nosocomial, molecular docking

### Introduction

Hospital-acquired nosocomial infection and drug resistance is a saddle in the health, medical field and this is a global health crisis (Patil and Rathod, 2020; Vakayil et al., 2021b). The antibiotic drugs are currently regained by the bioactive compounds of plants (Ansari et al., 2019) in this approach, the *B. serrata* achieves its significant place and exploring its usefulness towards antibacterial activity. The ancient (pre-historical) times used Boswellic acid contain infinite bioactives that are pharmacologically used for therapeutics (Sharma et al., 2016). *B. serrata* was well known in herbal treatment hundred years ago. Boswellic acid consists of two components  $\alpha$  and  $\beta$  boswellic acid originating from resin, which is the primary component of *B. serrata*. Resin from the

bark of the tree is rich in antioxidants. *B. serrata* is commonly known as Indian frankincense or Indian olibanum because the dried exudates from the bark of the tree are an ole-gum-resin. Dried gum looks like lumps or tears and is ivory (yellow and white) in colour. ‘Pure incense’ is another name for *B. serrata* derived from the French language. Olibanum means white or cream derived from Arabic languages so it is named as “olibanum”. The bioactive compounds offer their effectiveness towards the ailments. In the antique era, the therapeutic value of natural medicine was unknown at global level. In modern days the numerous researcher studies explored the economical and therapeutic significance of this species (Niphadkar et al., 2017). The pharma of plants probed the importance of the species implicit, enormously cultivated medicinal properties wide-ranging of bioactive compounds are obtaining best prognosis (Fan et al., 2021; Sun et al., 2021). According to the agriculture sector, the production of *B.serrata* is not adequate, but somehow it reduces the virulence of the organism causing disease. Whatever ailments occur to our body boswellic acid is the right choice (Niphadkar and Rathod, 2018). Thus, the salai gaugal heals inflammation, breathlessness, blood disorders, painful joints, heart, inability, malignants, and stomach upsets. In silico approach such as auto dock vena tool also helps us to briefly clarify the drug molecule and the receptor interactions by three-dimensional structures and its efficacy are exposed in the form of binding energies thus the healing process of an apparent wound (Chou et al., 2017) is preciously and powerfully treated and attained an expectational result by this phytotherapy which was conjoint with metal microparticles.

## Methodology

### Resin collection

Purchased wrinkled, golden amber-colored *B. serrata* resins from Kolli Hills, Namakkal DT, Tamil Nadu, India. After surface sterilization, it was dried in the shadow and then made into powder for extraction (Vakayil et al., 2021a).

### Extraction of *B. serrata*

10 g of powdered resin was weighed and mixed with 100 ml of hydroethanolic and aqueous solvent in a 250 ml flask. Through the microwave method, it was extracted by placing the beaker on the circular plate. Maintaining the different parameters such as temperature and time the aqueous phase was obtained after filtering via Whatman filter paper no1 (Kumar et al., 2016). After that, the crude was placed in an icebox, and the container was sealed for future analysis.

### GC-MS

Samples (solid and liquid) in GC–MS were prepared by dissolving inappropriate solvents (polar and nonpolar). International union of pure and applied chemistry (IUPAC) of the compound, Morphology, Molecular weight (MW), length, and internal diameter all are analyzed using the mass spectral library (NIST software) (Bhutada et al., 2017).

### Collection of strains

Sufficient exudates of the wound and skin specimens using sterile needles, containers, and tubes, were procured from chronic wound beds without cross-

contamination (Ohemu et al., 2018). Nearly twenty samples were collected from different laboratories in Namakkal DT, Tamil Nadu, India. Then sealed aseptically and transported to the laboratory in time (Kabeerdass et al., 2021).

### ***Inoculation and screening***

Isolation of the sample is done by inoculating it in their selective media such as MSA, and EMB and incubated at 37 °C for 24 h (Asante-Kwatia et al., 2020). Smear was prepared for gram staining to observe the morphology of the organism. Crystal violet, mordant, alcohol, and safranin are sprinkled one after the other for a minute, dried, and observed under the microscope to note whether it was a gram +ve or gram -ve. To confirm its physiological state some biochemical tests like Methylred, Voges Proskauer, indole, citrate oxidase, urease coagulase, and catalase were done (Vakayil et al., 2019).

### ***Antibiotic sensitivity test***

In the MHA plate, both gram-positive (*S. aureus*) and gram-negative (*K. oxytoca*) were streaked in a zig-zag manner on the plate. A circular antibiotic disc (6 mm) was impregnated on the plate (Vahabi et al., 2019). The plate was spread with *K. oxytoca* and *S. aureus* (nosocomial pathogens) against a spectrum of drugs such as Meropenem, vancomycin, and tetracycline (Abirami and Maghimaa, 2019).

### ***Antibacterial activity***

A diverse concentration of resin crude (20 µg, 40 µg, and 60 µg) was added to each well which was made by the cork Borell of 6 mm, then incubated for 24 h and the MIC values were observed and tabulated (Maghimaa and Alharbi, 2020; Arora et al., 2020; Kabeerdass et al., 2021; Vakayi et al., 2021f).

### ***Ligand preparation***

The structural (Schmiech et al., 2019) geometry in GC-MS were observed through the database and some chemical parameters like bond length, ionization energy, radius, efficient charges, strengths were ruled out (Khan et al., 2016). The efficacy of the antibiotics used and the three-dimensional structures of the compounds were identified in PDF format via molecular docking.

### ***Molecular docking***

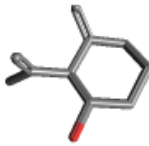
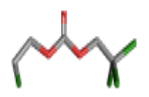
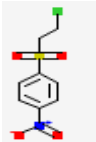
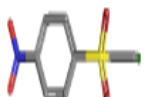
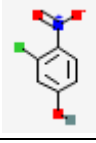
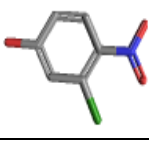
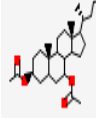
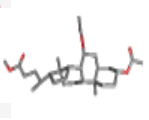
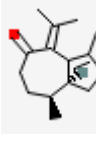
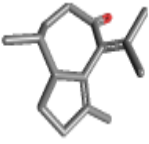
Docking was used to calculate the protein-ligand chemistry (Taghizadeh et al., 2018), torsion of the atom, van der Waals forces, its positions, the conjoining of the hydrogen atom (Du et al., 2015) between the un polar structure through the in silico mol soft tool Autodock vena (Bairwa and Jachak, 2016; Bolbolian et al., 2018; Vakayil et al., 2021d; Gaillard, 2018; Baburam et al., 2021).

## **Results**

### ***GC-MS analysis***

A stream of seven plant-derived compounds in the hydroethanolic extract from the crude of *B. serrata* via GC-MS is shown in Table 1.

**Table 1.** Phyto bioactive Compounds identified through GC–MS analysis of *B. serrata*

| S. No | Name of the compound                                                                    | Retention time | Molecular formula                                            | Molecular weight | Peak area | PUB CHEM ID | 2D structure                                                                          | 3D structure                                                                          |
|-------|-----------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------|------------------|-----------|-------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| 1.    | o-Mentha-1(7),8-dien-3-ol                                                               | 21.352         | C <sub>10</sub> H <sub>16</sub> O                            | 152.23 g/mol     | 2.67      | 564552      |    |    |
| 2.    | Carbonic acid, 2-chloroethyl 2,2,2-trichloroethyl ester                                 | 22.063         | C <sub>5</sub> H <sub>6</sub> Cl <sub>4</sub> O <sub>3</sub> | 255.9 g/mol      | 1.26      | 87646995    |    |    |
| 3.    | Benzene, 1-[(2-chloroethyl)sulfonyl 4-nitro                                             | 22.130         | C <sub>8</sub> H <sub>8</sub> ClNO <sub>4</sub> S            | 249.67 g/mol     | 1.07      | 80935       |    |    |
| 4.    | 3-chloro-4-nitrophenol                                                                  | 26.318         | C <sub>6</sub> H <sub>4</sub> ClNO <sub>3</sub>              | 173.55 g/mol     | 1.62      | 10283       |    |    |
| 5.    | Cholan-24-oic acid, 3,12-bis(acetyloxy)                                                 | 26.729         | C <sub>29</sub> H <sub>46</sub> O <sub>6</sub>               | 490.7 g/mol      | 8.88      | 21140628    |   |   |
| 6.    | Pyrene, hexadecahydro-                                                                  | 26.840         | C <sub>16</sub> H <sub>26</sub>                              | 218.38 g/mol     | 12.13     | 75524       |  |  |
| 7.    | 5(1H)-Azulenone, 2,4,6,7,8,8a-hexahydro-3,8-dimethyl-4-(1-methylethylidene)-, (8S-cis)- | 27.229         | C <sub>15</sub> H <sub>22</sub> O                            | 218.33 g/mol     | 45.36     | 91735354    |  |  |

### Observed bioactive compounds in the extract

Bioactive compounds examined were o-Mentha-1(7),8-dien-3-ol, Carbonic acid, 2-chloroethyl 2,2,2-trichloroethyl ester, Benzene, 1-[(2-chloroethyl)sulfonyl 4-nitro, 3-chloro-4-nitrophenol, Cholan-24-oic acid, 3,12-bis(acetyloxy), Pyrene, hexadecahydro-, and 5(1H)-Azulenone, 2,4,6,7,8,8a-hexahydro-3,8-dimethyl-4-(1-methylethylidene)-, (8S-cis)-s, the results are briefly given in Table 1. The docking score with the minimal binding energy of Cholan-24-oic acid, 3,12-bis(acetyloxy) shows -7.6 of BF (kcal/mol) with AmpC from *K. oxytoca* is explained in Table 5.

### Isolation and identification

Dark pink shiny mucoid lactose fermenting colonies were isolated on McConkey agar plate which differ from other commensals. This is an encapsulated gram-negative bacillus that shows positive sign for Indole, Voges Proskauer, urease, citrate, catalase,

and for gram-positive cocci positive results were obtained to VP, Citrate, Urease, catalase, coagulase methyl red, and oxidase.

### Antibiotic sensitivity

An extensive spectrum of antibiotics such as tetracycline (30 µg), Chloramphenicol (30 µg), and Gentamycin (10 µg) were effectively used against gram-negative bacilli *K. oxytoca* and also *S. aureus* which is a gram-positive coccus. In this *K. oxytoca* showed a high zone of inhibition (21 mm, and 23 mm) against tetracycline than chloramphenicol when compared with gram-positive bacilli *S. aureus* with a zone of inhibition (28 mm, and 16 mm) the results are presented in Table 2.

**Table 2.** Antibiotic sensitivity test against the nosocomial pathogens (ZOI in mm)

| Isolates                     | Tetracycline (30 µg) |     | Chloramphenicol (30 µg) |     | Gentamycin (10 µg) |     |
|------------------------------|----------------------|-----|-------------------------|-----|--------------------|-----|
|                              | ZOI                  | Inf | ZOI                     | Inf | ZOI                | Inf |
| <i>Staphylococcus aureus</i> | 28                   | S   | 16                      | R   | 21                 | S   |
| <i>Klebsiella oxytoca</i>    | 21                   | S   | 23                      | S   | 14                 | R   |

R – Resistance, I – Intermediate, S – Sensitivity, ZOI – Zone of Inhibition, Inf – Inference Te; Tetracycline: C; Chloramphenicol; Gm: Gentamycin

### Antibacterial activity

In the case of resin crude, the aqueous and hydroethanolic extract of the nosocomial pathogen *K. oxytoca* and *S. aureus* shows the highest zone of inhibition of 18 mm at 60 µg concentration. This indicates the susceptibility of pathogens towards the extracts, their MIC values are shown in Table 3.

**Table 3.** *B. serrata* shows susceptibility against the nosocomial pathogens

| S. no | Isolates                     | <i>B. serrata</i> resin extracts (ZOI in mm) |            |            |                               |            |            |
|-------|------------------------------|----------------------------------------------|------------|------------|-------------------------------|------------|------------|
|       |                              | Aqueous extract (in mcg)                     |            |            | Hydroethanol extract (in mcg) |            |            |
|       |                              | 20                                           | 40         | 60         | 20                            | 40         | 60         |
| 1     | <i>Staphylococcus aureus</i> | 15 ± 1.041                                   | 17 ± 0.763 | 18 ± 0.763 | 17 ± 0.763                    | 18 ± 0.763 | 18 ± 0.763 |
| 2     | <i>Klebsiella oxytoca</i>    | 13 ± 0.557                                   | 16 ± 0.771 | 18 ± 0.763 | 14 ± 1.041                    | 15 ± 1.04  | 18 ± 0.763 |

Data are mean ± SE (n = 3)

### Protein-protein interaction

Antibiotic Reference Drugs used for docking are shown in Table 5. Nonbonding and bonding interaction of the residues in the active site is shown via docking (Table 4). The AmpC from *K. oxytoca* shows a binding affinity at -7.6 (less binding energy) with Cholan-24-oic acid, 3,12-bis(acetyloxy), followed by Pyrene, hexadecahydro- -7.5 (kcal/mol) and 5(1H)-Azulenone, 2,4,6,7,8,8a-hexahydro-3,8-dimethyl-4-(1-methylethylidene)-, (8S-cis)- -6.7 (kcal/mol). Among the Phyto compounds, Cholan-24-oic acid, 3,12-bis(acetyloxy), show a binding affinity -7.6 (kcal/mol), and the reference drug tetracycline also has the same binding affinity -7.6 (kcal/mol) are shown by highlighting in Table 5. The binding score and 3D graphical structure are all shown

below with their CID 21140628 > CID 75524 > CID 91735354 > CID 54675776 in which the color variation shows the binding affinity of the amino acids in Figures 1-4.

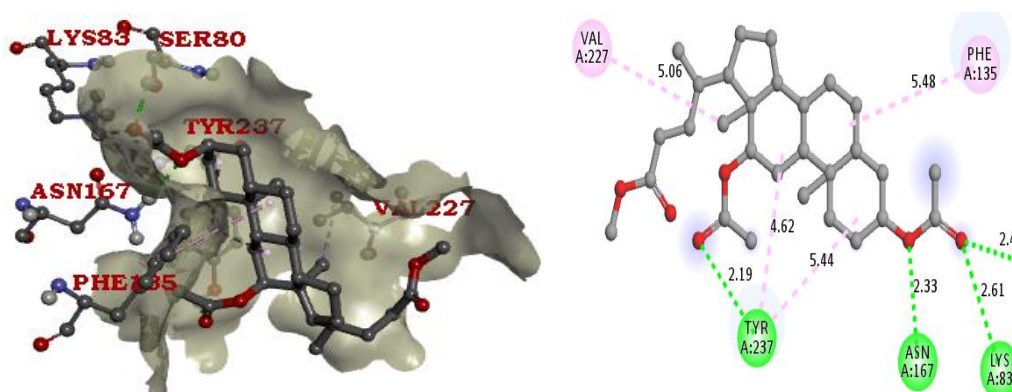


Figure 1. AmpC K. oxytoco - CID 21140628 docking pose & interaction plot (-7.6 Kcal/mol)

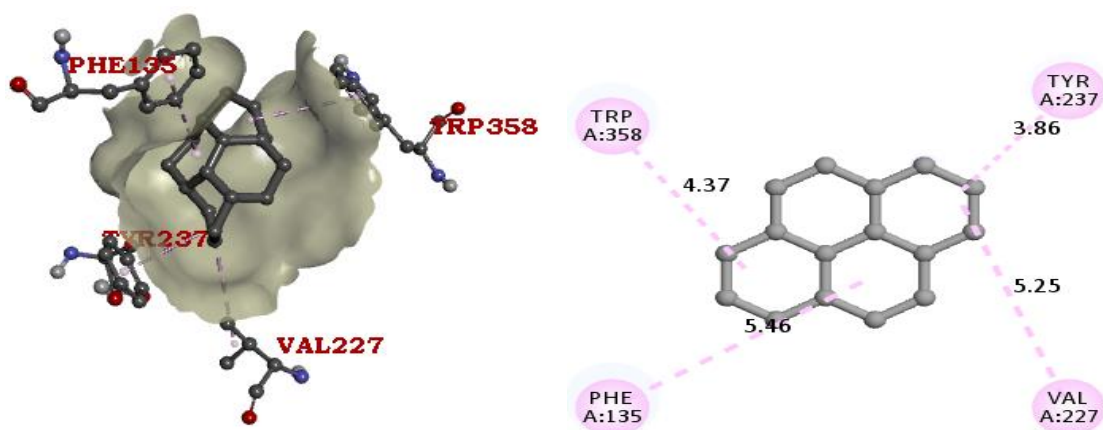


Figure 2. AmpC K. oxytoco - CID 75524 docking pose & interaction plot (-7.5 Kcal/mol)

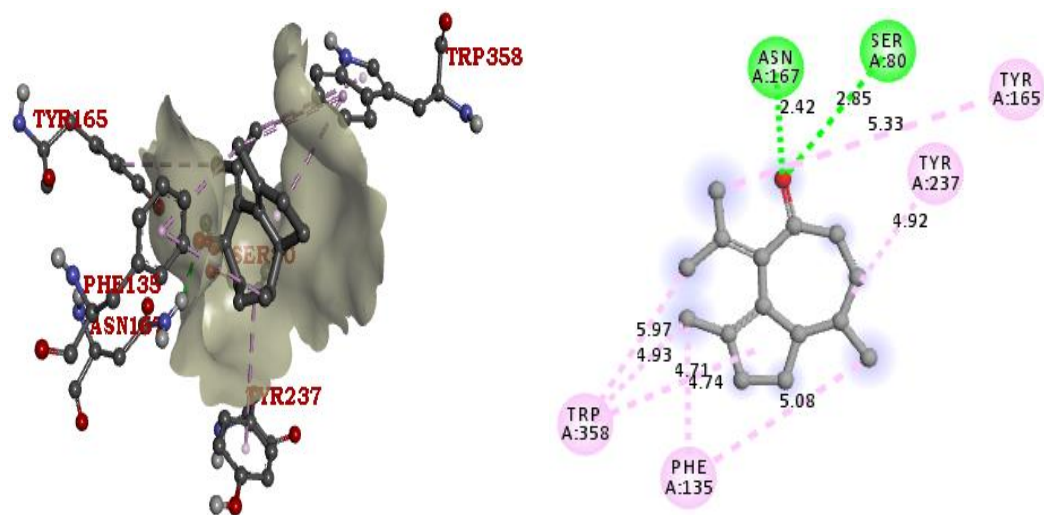
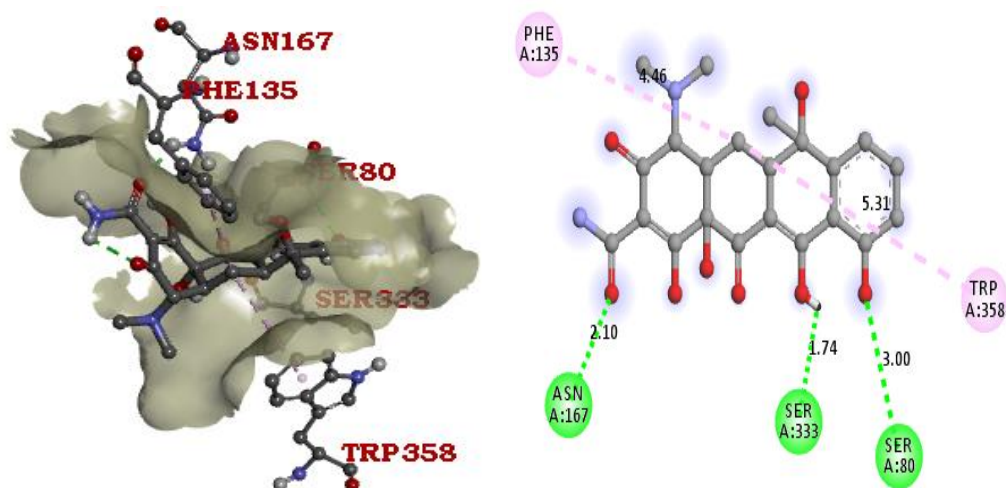


Figure 3. AmpC K. oxytoco - CID 91735354 docking pose & interaction plot (-6.7 Kcal/mol)



**Figure 4.** AmpC *K. oxytoco* - CID 54675776 docking pose & interaction plot (-7.6 Kcal/mol)

**Table 4.** Docking interaction table for AmpC *K. oxytoco* ligand complexes

| S. No | Complex name | Bonded interactions       | Non bonded interactions     | Docking score (-K.Cal/mol) |
|-------|--------------|---------------------------|-----------------------------|----------------------------|
| 1.    | CID 564552   | -                         | Met306,Leu134,Phe135,Tyr165 | -5.4                       |
| 2.    | CID 87646995 | Ser80,Ser333              | Ser333                      | -4.5                       |
| 3.    | CID 80935    | Asn167,Thr331             | Gly305,Ser80,Phe135         | -5.8                       |
| 4.    | CID 10283    | Ala234,Phe185,Asp233      | Leu232,Glu235               | -5.2                       |
| 5.    | CID 21140628 | Ser80,Lys83,Asn167,Tyr237 | Phe135,Val227,Tyr237        | -7.6                       |
| 6.    | CID 75524    | -                         | Phe135,Val227,Tyr237,Trp358 | -7.5                       |
| 7.    | CID 91735354 | Ser80,Asn167              | Phe135,Ytr165,Tyr237,Trp358 | -6.7                       |
| 8.    | CID 5959     | -                         | Ser333,Tyr237               | -6.8                       |
| 9.    | CID 37569    | Ser333,Ser80,Val136       | Asn167                      | -6.6                       |
| 10.   | CID 54675776 | Ser80,Asn167,Ser333       | Phe135,Trp358               | -7.6                       |

**Table 5.** Docking score of phytocompounds and antibiotic reference drug against AmpC

| Compounds                                                                               | Binding affinities (kcal/mol) with AmpC from <i>K. oxytoca</i> |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------|
| o-Mentha-1(7),8-dien-3-ol                                                               | -5.4                                                           |
| Carbonic acid, 2-chloroethyl 2,2,2-trichloroethyl ester                                 | -4.5                                                           |
| Benzene, 1-[(2-chloroethyl)sulfonyl 4-nitro                                             | -5.8                                                           |
| 3-chloro-4-nitrophenol                                                                  | -5.2                                                           |
| Cholan-24-oic acid, 3,12-bis(acetyloxy)                                                 | -7.6                                                           |
| Pyrene, hexadecahydro-                                                                  | -7.5                                                           |
| 5(1H)-Azulenone, 2,4,6,7,8,8a-hexahydro-3,8-dimethyl-4-(1-methylethylidene)-, (8S-cis)- | -6.7                                                           |
| Chloramphenicol                                                                         | -6.8                                                           |
| Gentamycin                                                                              | -6.6                                                           |
| Tetracyclin                                                                             | -7.6                                                           |

## Discussion

Nosocomial drug resistance developed a rigorous crisis in health and hospital care, intensifying morbidity, fatality, extent the reside and raise the costs of healthcare (Exner et al., 2017). The nosocomial drug resistance exhibited variations among hospitals

around the globe. The majority of the infections caused by bacteria are resistant to multiple drugs (Asres et al., 2017). This study explored the drug resistance of *S. aureus* and *K. oxytoca* from nosocomial infections. Similar findings were explored by other studies (Vakayil et al., 2020). This determined that drug resistance to nosocomial pathogens is a major health issue. A lofty number of patients, deprived infection management practices, self-therapeutic medication, maltreatment, improper overprescription, extended hospitalization, and deviation in aseptic dealings may be the causes. The crude of the *B. serrata* resin shows its inhibitory action against the nosocomial pathogen *K. oxytoca* (Jamwal and Sharma, 2018). *B. serrata* consists of immense therapeutic bioactive that diverge by the extraction process and compound nature. The small organic chemical compound obtained by microwave extraction shows its effective role in antibacterial, antifungal, ulcer healing, and control of nosocomial infection (Beghelli et al., 2017). Through GC-MS analysis the effective bioactive compound cholan-24-oic acid, 3,12-bis(acetyloxy) (Vakayil et al., 2021c; Perleberg et al., 2018) was extracted and proved its susceptibility character against tetracycline, chloramphenicol, and gentamycin via in silico tool (Siemoneit et al., 2017).

## Conclusion

The phytochemicals in *B. serrata* are efficient in repairing the wound. Morphology and biochemical changes occur in the wound which leads to scar formation after exposure to the *B. serrata* extract. Protein-protein interaction of the nosocomial pathogen (*K. oxytoca*) against tetracycline, chloramphenicol, and gentamycin showed less effectiveness compared with the action of *B. serrata* extract. This proves that *B. serrata* is a cheap, eco-friendly, and safe remedy due to the rich source of antioxidant properties. In the future, it might be produced on a large scale and act as a medication for curing chronic ulcers.

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**Conflict of interests.** The authors declare no conflict of interests with this research.

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