Original Research Article

**In vitro evaluation of antibacterial activity of verbascoside, lemon verbena extract and caffeine in combination with gentamicin against drug-resistant *Staphylococcus aureus* and *Escherichia coli* clinical isolates**

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**Abstract**

**Objective:** In recent years, there has been an increasing interest in using herbal products to overcome bacterial resistance. The aim of this study was to investigate the effect of lemon verbena aqueous extract, verbascoside and caffeine in combination with gentamicin against standard and clinical isolates of *Staphylococcus aureus* and *Escherichia coli* strains.

**Materials and Methods:** The MIC and MBC values of different antibacterial agents against bacterial strains were determined. The effect of co-administration lemon verbena extract, verbascoside, and caffeine and gentamicin was studied *in vitro* using a checkerboard method and calculating fraction inhibitory concentration index (FICI).

**Results:** Herbal extract, verbascoside and caffeine alone showed no inhibitory effects on any of the bacterial strains (at doses up to 200 μg/ml). Herbal extract, verbascoside and caffeine were able to decrease the MIC of gentamicin against the standard resistant strains and two clinical isolates. Among these combinations, the co-administration of verbascoside and gentamicin was more effective and synergistic activities (FICI<1) against clinical isolates were observed.

**Conclusion:** The results of the present study revealed that herbal extract, verbascoside and caffeine potentiated the antimicrobial action of gentamicin against some clinical isolates of *S. aureus* and *E. coli*.

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Introduction

Anti-bacterial resistance is one of the greatest challenges of the twenty-first century (Rasko and Sperandio, 2010). Infectious diseases caused by resistant strains have numerous negative effects as their treatment requires higher doses of antibiotics, additional treatments, and prolonged hospitalizations and causes higher mortality rates (Khameneh et al., 2016).

Recently, many strategies have been proposed to combat bacterial resistance. Developing novel structural and functional classes of antibiotics, combination therapy, applying natural compounds and using novel drug delivery systems are the main approaches in this field (Khameneh et al., 2015).

Combination therapy has several potential advantages including enhancing the antibiotic activity, preventing the emergence of resistance and reducing the risk of infection (Hagihara et al., 2012). Therefore, various compounds have been tested in combination with antibiotics. These days, the investigators' attention is increasingly attracted to natural compounds which have shown potent antibacterial activities when used alone or in combination with other antibacterial agents (Akaberi et al., 2015, Forouzanfar et al., 2014).

*Lippia citriodora* (lemon verbena) has been widely used in traditional medicine for its pharmacological properties such as antispasmodic, antipyretic, sedative, and digestive activities (Carnat et al., 1999, Quirantes-Pine et al., 2013). *L. citriodora* leaves contain many polar compounds like phenyl propanoids, flavonoids, phenolic acids and iridoid glycosides (Quirantes-Pine et al., 2013).

Verbascoside has been mainly found in the *Verbascum* species but has also been detected in more than 200 plant species (Alipieva et al., 2014). This compound is the major substance in lemon verbena and has several properties such as anti-inflammatory, antioxidant, antitumor and antimicrobial activities (Quirantes-Pine et al., 2013). Verbascoside is a member of the phenylpropanoid glycosides family which is structurally characterized by the caffeic acid moiety and 4,5-hydroxyphenylethanol (hydroxytyrosol) bound to a β-(d) glucopyranoside, through ester and glycosidic links, respectively, with a rhamnose in sequence (1–3) to the glucose molecule (Singh et al., 2010).

The antibacterial activities of lemon verbena extract and verbascoside have received a great deal of attention (Ghaemi et al., 2007). The ability of plants rich in verbascoside for treatment of microbial infections, has been previously described (Georgiev et al., 2012). It has been reported that verbascoside can be a promising therapeutic agent for treatment of microbial infections. In another study, the efficacy of verbascoside for treatment of acne vulgaris was mentioned (Azimi et al., 2012).

The mechanism of antibacterial action of verbascoside is not fully understood but the capability of verbascoside to modulate membrane-dependent cellular processes might be involved in its antibacterial action (Funes et al., 2010).

Combination of chemical compounds with antibacterial agents is another effective approach. Methylxanthines are potent bronchodilators used to treat acute asthma. Moreover, there is some evidence that these compounds show antibacterial properties against some bacterial pathogens (Elgaher et al., 2009, Hayallah et al., 2011). Aminophylline and caffeine, for instance, increased the antimicrobial action of carbenicillin, ceftizoxime and gentamicin against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Hosseinzadeh et al., 2006). Also, caffeine has shown antibacterial properties along with potent antifungal activity against *Candida albicans* (Gyawali et al., 2014, Kim et al., 2013).

Gentamicin is a potent antibiotic which has been used for the treatment of a wide range of infections caused by Gram-
positive and Gram-negative bacteria (Corvec et al., 2013, Pantosti et al., 2007). Despite all advantages, this antibiotic suffers from some shortcomings such as undesirable side effects and increased microbial resistance. In this regard, combination of gentamicin with other antibacterial agents may reduce the risk of increasing resistance and toxicity.

The aim of the present study was to evaluate the antibacterial activities of caffeine, lemon verbena extract and verbascoside alone and in combination with gentamicin against two clinically important bacteria namely, *Escherichia coli* and *S. aureus*.

**Materials and Methods**

**Materials**

*L. citriodora* leaves were collected from the surrounding areas of Karaj city, Alborz province, Iran, dried in shadow and grounded to powder. *L. citriodora* was identified by the Department of Botany Ferdowsi University (Mashhad, Iran), and voucher samples were preserved in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Verbascoside was purchased from Extrasynthese (Genay, France). Caffeine and gentamicin were obtained from Hakim Pharmaceutical Company (Tehran, Iran).

**Preparation of *L. citriodora* aqueous extract**

The aqueous extract of *L. citriodora* was prepared by adding 1 L of distilled water to 100 g of powdered plant material in a 2.5 L glass flask and boiled for 15 min. The solution was subsequently filtered using Whatman No. 1 filter paper and the obtained residue was stored in a freezer at −70°C and then freeze-dried.

**Bacterial strains**

The microorganisms used in this study were *S. aureus* (five strains including one methicillin-resistant strain [MRSA ATCC 43300] and four isolated strains) and *E. coli* (two isolated strains). *S. aureus* were isolated from acne (two strains), eye and urinary tract infections.

**Determination of minimum inhibitory and minimum bactericidal concentrations of antibacterial agents**

The minimum inhibitory concentration (MIC) of extracts and compounds against bacteria was determined as previously described (Khameneh et al., 2015). Briefly, approximately 10⁶ CFU/ml cells from overnight cultures were used as inoculum. Serial dilutions of each tested compound were prepared in Muller Hinton Broth (MHB) (Difco) in 96-well microtiter plates. Then, the inoculum was added to each well to obtain a final bacterial concentration of 10⁵ CFU/ml. The inoculated microplates were incubated at 37 °C for 24 hr under aerobic condition. MIC was determined by adding TTC (triphenyl tetrazolium chloride, Merck) to each well at a concentration of 0.05% followed by incubation at 37 °C for 30 min. MICs were defined as the lowest concentration of tested compound that did not reduce TTC to red formazan.

For MBC determination, an aliquot of 10 μl from all wells with no visible growth (no red color), was seeded in Tryptone Soya Agar plates (TSA) (Lab M; Bury, UK). The plates were then incubated at 37°C, overnight. MBC is defined as the lowest concentration of antimicrobial agent that kills >99.9% of bacteria.

**Evaluation of synergistic effect**

To evaluate the antibacterial activities of two antibacterial agents, the checkerboard method was used. In brief, serial 2-fold dilutions of gentamicin and other antimicrobial agents were mixed in each well of a 96-well microtiter plate (250 μL). So, each row and column contained a constant amount of one antibacterial agent and increasing amounts of the second agent. The MIC was assessed as mentioned above and finally the Fractional Inhibitory Concentration
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Index (FICI) value was used to assess whether synergism, indifference or antagonism occurred following the co-administration of the two evaluated antibacterial agents (Khameneh et al., 2015).

The FICI of the antibacterial agent combination was FIC of drug A + FIC of drug B, where the FIC of drug A= (MIC of drug A in combination)/(MIC of drug A alone) and the FIC of drug B= (MIC of drug B in combination)/(MIC of drug B alone). The combination effects were evaluated based on the following criteria: FICI<0.5 denoting synergy; 0.5< FICI >0.75 denoting partial synergy; 0.76< FICI <1 denoting an additive effect; 1< FICI <4 denoting indifference; and FICI >4 denoting antagonism (Khameneh et al., 2015).

Statistical analysis
All tests were performed at least in triplicate. A one-way analysis of variance (ANOVA) was used for testing overall group differences. Differences between mean were statistically considered significant if the p value was less than 0.05.

Results
Determination of MIC and MBC
The MIC and MBC values of gentamicin for each clinical isolate or reference bacteria were noted in Table 1. MIC and MBC of other tested compounds were higher than 200 μg/ml.

Table 1. MIC values of gentamicin against 7 clinically resistant Staphylococcus aureus and Escherichia coli strains.

| Strain                   | MIC/MBC (μg/ml) |
|--------------------------|-----------------|
| Staphylococcus aureus    |                 |
| 1                        | >80             |
| 2                        | >20             |
| 3                        | >80             |
| 4                        | >80             |
| 5                        | 50              |
| Escherichia coli         |                 |
| 1                        | >80             |
| 2                        | 50              |

Evaluation of synergistic effect
The combined effects of gentamicin and the different compounds were shown in Tables 2-4.

These results indicated that combination of gentamicin and caffeine was not effective against bacterial strains except for only one clinical isolate (S. aureus No.2).

According to the results (Tables 3 and 4), it was concluded that combination of gentamicin with natural compounds, results in partial synergistic effects. For instance, combination of gentamicin with lemon verbena extract was effective against some strains of E. coli and S. aureus. It should be noted that combination of gentamicin with natural product such as verbascoside was more effective in comparison with mono-antibiotic therapy.

Table 2. Results of application of a combination of gentamicin and caffeine against Staphylococcus aureus and Escherichia coli.

| Bacterial strains         | Strain     | Agent      | MIC (μg/ml) | FICI | Outcome     |
|---------------------------|------------|------------|-------------|------|-------------|
| Staphylococcus aureus     | 1          | gentamicin | >80         | 1    | Indifference|
|                           |            | caffeine   | >80         | 1    | Indifference|
|                           | 2          | gentamicin | >20         | 0.5  | Partial synergy|
|                           |            | caffeine   | >20         | 0.06 | Indifference|
|                           | 3          | gentamicin | >80         | 1    | Indifference|
|                           |            | caffeine   | >80         | 1    | Indifference|
|                           | 4          | gentamicin | >20         | 1    | Indifference|
|                           |            | caffeine   | >20         | 1    | Indifference|
|                           | 5          | gentamicin | >20         | 1    | Indifference|
|                           |            | caffeine   | >20         | 1    | Indifference|
| Escherichia coli          | 1          | gentamicin | >80         | 1.25 | Indifference|
|                           |            | caffeine   | >80         | 1    | Indifference|
|                           | 2          | gentamicin | >20         | 1    | Indifference|
|                           |            | caffeine   | >20         | 1    | Indifference|

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Discussion

Clinically-isolated bacteria are regarded as main causes of nosocomial infections. These types of infections pose serious threats to the public health and a cause wide range of problems. So, finding a proper solution seems to be important. Combination therapy is an effective approach to reduce the risk of nosocomial infection which is currently attracting marked attention. Therefore, in the present study, different combinations of gentamicin and some therapeutic agents were evaluated.

The MIC and MBC values of gentamicin against bacterial species (Table 1) indicated that with respect to the standard strain (MRSA ATCC 43300), isolated species were more resistant to antimicrobial agents. These evidence reflected that the bacterial species used in this study, sh owed high levels of resistance to antibacterial agents. To enhance the antibacterial activity, three compounds were used in combination with gentamicin.

Methylxanthines are useful therapeutic agents administered for treatment of acute asthma. These agents were also used for treatment of bacterial infections (Bazzaz et al., 2012, Hosseinzadeh et al., 2006). In the present study, the combinatorial effect of caffeine and gentamicin against bacterial species were investigated (Table 2). According to our data, the synergistic effects were only observed against one clinical isolate of S. aureus. These findings supported that caffeine might be more efficient against Gram-positive bacteria compared to Gram-negative ones. These results were in line with previously

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**Table 3.** Results of application of a combination of gentamicin and lemon verbena extract against *Staphylococcus aureus* and *Escherichia coli*.

| Bacterial strains     | Strain | Agent                  | MIC (μg/ml)                  | FIC | FICI | Outcome   |
|-----------------------|--------|------------------------|------------------------------|-----|------|-----------|
| *Staphylococcus aureus* | 1      | gentamicin             | >80                          | >80 | 1    | Indifference |
|                       |        | lemon verbena extract  | >200                         | >80 | 1    | Indifference |
|                       | 2      | gentamicin             | 12.5                         | 6.25| 0.5  | 0.51 Partial synergy |
|                       |        | lemon verbena extract  | >200                         | 3.1 | 0.06 | Indifference |
|                       | 3      | gentamicin             | >80                          | >80 | 1    | Indifference |
|                       |        | lemon verbena extract  | >200                         | >80 | 1    | Indifference |
|                       | 4      | gentamicin             | >80                          | >80 | 1    | Indifference |
| *Staphylococcus aureus* (MRSA ATCC 43300) | 5  | gentamicin             | 50                           | 50  | 1    | Indifference |
| *Escherichia coli*     | 1      | gentamicin             | >80                          | >80 | 1    | Indifference |
|                       |        | lemon verbena extract  | >200                         | >80 | 1    | Indifference |
|                       | 2      | gentamicin             | 50                           | 25  | 0.5  | 0.75 Partial synergy |
|                       |        | lemon verbena extract  | >200                         | 50  | 0.25 | Indifference |

**Table 4.** Results of application of a combination of gentamicin and verbascoside against *Staphylococcus aureus* and *Escherichia coli*.

| Bacterial strains     | Strain | Agent                  | MIC (μg/ml)                  | FIC | FICI | Outcome   |
|-----------------------|--------|------------------------|------------------------------|-----|------|-----------|
| *Staphylococcus aureus* | 1      | gentamicin             | >80                          | >80 | 1    | Indifference |
|                       |        | verbascoside           | >200                         | >80 | 1    | Indifference |
|                       | 2      | gentamicin             | 12.5                         | 6.25| 0.5  | 0.75 Partial synergy |
|                       |        | verbascoside           | >200                         | 50  | 0.25 | Indifference |
|                       | 3      | gentamicin             | >80                          | >80 | 1    | Indifference |
|                       |        | verbascoside           | >200                         | >80 | 1    | Indifference |
|                       | 4      | gentamicin             | >80                          | >80 | 1    | Indifference |
| *Staphylococcus aureus* (MRSA ATCC 43300) | 5  | gentamicin             | 50                           | 25  | 0.5  | Additive |
| *Escherichia coli*     | 1      | gentamicin             | >80                          | >80 | 1    | 1.25 Indifference |
|                       |        | lemon verbena extract  | >200                         | 100 | 0.5  | Additive |
|                       | 2      | gentamicin             | 50                           | 25  | 0.5  | 0.53 Partial synergy |
|                       |        | lemon verbena extract  | >200                         | 6.25| 0.03 | Partial synergy |

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published data which showed that some derivatives of methylxanthines exert antibacterial activates especially against Gram-positive species (Elgaher et al., 2009). Additionally, it was shown that concomitant intake of the antibiotics and caffeine potentiated the antibacterial effect of antibiotics against S. aureus (Esimone et al., 2008).

These evidence support the hypothesis that extracts with high levels of verbascoside can show the antibacterial activities. In previous studies, the antibacterial properties of Arrabidaea harleyi A.H. Gentry extracts containing verbascoside, were proven (Lima et al., 2003). Also, it was shown that herbal extracts which contain flavonoids, alkaloids, tannins and phenolic compounds, affect the efflux system of bacteria (Coutinho et al., 2009). These findings were consistent with our data (Table 3). The combination of gentamicin with lemon verba extract enhanced antibacterial activities of antibiotics. These results support some ethnopharmacological uses of this plant (Lima et al., 2003).

Buddleja globosa leaves showed antibacterial activity against S. aureus and E. coli. Based on the antimicrobial activity, the extract was fractionated and verbascoside was isolated (Pardo et al., 1993). Verbascoside belongs to the phenylpropanoid glycosides family with demonstrate anti-inflammatory, antioxidant, antitumor and antimicrobial properties (Alipieva et al., 2014, Pardo et al., 1993). As seen in Table 4, upon combination of gentamicin with verbascoside, partial synergistic activities were observed in some clinical isolates of S. aureus and E. coli. In case of standard strain, additive effects were seen. Additionally, in comparison with lemon verba extract, the antibacterial activity of verbascoside was more pronounced. These data indicated that pure compounds such as verbascoside showed better activity than herbal extracts. These findings were also

in line with previous findings which showed that verbascoside has antibacterial activities (Alipieva et al., 2014). The antibacterial action of verbascoside was not fully understood, but it was suggested that it is related to inhibition of leucine uptake and bacterial protein synthesis (Guillermo Avila et al., 1999). It was demonstrated that verbascoside was more effective against Gram-positive bacteria and this effect was due to perturbing the phospholipid/water interface of membranes and consequently increasing the surface area of the phospholipid head groups in the bilayers (Funes et al., 2010).

The results of this in vitro study highlighted the advantages of antibiotic combination with natural and chemical compounds. This approach can be used as a promising solution for combating bacterial infections.

Conflict of interest
The authors have no conflict of interests to declare.

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References
Akaberi M, Iranshahy M, Iranshahi M. 2015. Review of the traditional uses, phytochemistry, pharmacology and toxicology of giant fennel (Ferula communis l. subsp. communis). Iran J Basic Med Sci, 18:1050-1062.
Alipieva K, Korkina L, Orhan IE, Georgiev MI. 2014. Verbascoside — A review of its occurrence, (bio) synthesis and pharmacological significance. Biotechnol Adv, 32: 1065-1076.
Azimi H, Fallah-Tafti M, Khakshur AA, Abdollahi M. 2012. A review of phytotherapy of acne vulgaris: perspective of new pharmacological treatments. Fitoterapia, 83:1306-17.
Bazzaz BS, Lavaei S, Hosseinzadeh H. 2012. Interaction of methylxanthines and gentamicin against Staphylococcus aureus and Pseudomonas aeruginosa: role of phosphodiesterase inhibition. Acta Microbiol Immunol Hung, 59:13-20.

Carnat A, Carnat AP, Fraisse D, Lamaison JL. 1999. The aromatic and polyphenolic composition of lemon verbena tea. Fitoterapia, 70:44-49.

Corvec S, Tafin UF, Betrisey B, Borens O, Trampuz A. 2013. Activities of fosfomycin, tigecycline, colistin, and gentamicin against extended-spectrum-lactamase-producing escherichia coli in a foreign-body infection model. Antimicrobial Agents Chemother, 57:1421-1427.

Coutinho HD, Costa JG, Lima EO, Falcao-Silva VS, Siqueira JP, Jr. 2009. Herbal therapy associated with antibiotic therapy: potentiation of the antibiotic activity against methicillin-resistant Staphylococcus aureus by Turnera ulmifolia L. BMC Complement Altern Med, 9:13.

Elgaher WA, Hayallah AM, Salem OIA, Abdel Alim AAM. 2009. Synthesis, anti-bronchoconstrictive, and antibacterial activities of some new 8-substituted-1,3-dimethylxanthine derivatives. Bulletin of Pharmaceutical Sciences, 32:153-187.

Esimone C, Okoye F, Nworu C, Agubata C. 2008. In vitro interaction between caffeine and some penicillin antibiotics against Staphylococcus aureus. Trop J Pharm Res, 7:969-974.

Forouzanfar F, Fazly Bazzaz BS, Hosseinzadeh H. 2014. Black cumin (Nigella sativa) and its constituent (thymoquinone): A review on antimicrobial effects. Iran J Basic Med Sci, 17:929-938.

Funes L, Laporta O, Cerdan-Calero M, Micol V. 2010. Effects of verbascoside, a phenylpropanoid glycoside from lemon verbena, on phospholipid model membranes. Chem Phys Lipids, 163:190-9.

Georgiev M, Pastore S, Lulli D, Alipieva K, Kostyuk V, Potapovich A, Panetta M, Korkina L. 2012. Verbascum xanthophoeniceum-derived phenylethanoid glycosides are potent inhibitors of inflammatory chemokines in dormant and interferon-gamma-stimulated human keratinocytes. J Ethnopharmacol, 144:754-60.

Ghaemi EO, Khorshidi D, Moradi A, Seifi A, Mazendranri M, Bazouri M, Mansourian AR. 2007. The efficacy of ethanolic extract of Lemon verbena on the skin infection due to Staphylococcus aureus in an animal model. Pak J Biol Sci, 10:4132-5.

Guillermo Avila J, De Liverant JG, Martínez A, Martínez G, Muñoz JL, Arciniegas A, Romo De Vivar A. 1999. Mode of action of Buddleja cordata verbascoside against Staphylococcus aureus. J Ethnopharmacol, 66:75-78.

Gyawali R, Adkins A, C. Minor R, Ibrahim SA. 2014. Behavior and changes in cell morphology of Escherichia coli O157:H7 in liquid medium and skim milk in the presence of caffeine. CYTA- J Food, 12:235-241.

Hagihara M, Crandon JL, Nicolau DP. 2012. The efficacy and safety of antibiotic combination therapy for infections caused by Gram-positive and Gram-negative organisms. Expert Opin Drug Saf, 11:221-33.

Hayallah AM, Elgaher WA, Salem OI, Abdel Alim AAM. 2011. Design and synthesis of some new theophylline derivatives with bronchodilator and antibacterial activities. Archives of Pharmacal Research, 34:3-21.

Hosseinzadeh H, Fazly Bazzaz BS, Moaddab Sadati M. 2006. In vitro evaluation of methylxanthines and some antibiotics: interaction against Staphylococcus aureus and Pseudomonas aeruginosa. Iran Biomed J, 10:163-167.

Khameneh B, Diab R, Ghazvini K, Fazly Bazzaz BS. 2016. Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. Microb Pathog, 95:32-42.

Khameneh B, Fazly Bazzaz BS, Amani A, Rostami J, Vahdati-Mashhadian N. 2015. Combination of anti-tuberculosis drugs with vitamin C or NAC against different Staphylococcus aureus and Mycobacterium tuberculosis strains. Microb Pathog, 93:83-87.

Kim YW, Chun HJ, Kim IW, Liu HB, Ahn WS. 2013. Antimicrobial and antifungal effects of green tea extracts against microorganisms causing vaginitis. Food Science and Biotechnology, 22:713-719.

Lima CSdA, Amorim ELCd, Sena KXdFR, Chiappeta AdA, Nunes XP, Agra MdF, da-Cunha EVL, Silva MSd, Barbosa-Filho JM.
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2003. Antimicrobial activity of a mixture of two isomeric phenylpropanoid glycosides from Arrabidaea harleyi AH Gentry (Bignoniaceae). Revista Brasileira de Ciências Farmacêuticas, 39:77-81.

Pantosti A, Sanchini A, Monaco M. 2007. Mechanisms of antibiotic resistance in Staphylococcus aureus. Future Microbiol, 2:323-334.

Pardo F, Perich F, Villarroel L, Torres R. 1993. Isolation of verbascoside, an antimicrobial constituent of Buddleja globosa leaves. J Ethnopharmacol, 39:221-2.

Quirantes-Pine R, Herranz-Lopez M, Funes L, Borras-Linares I, Micol V, Segura-Carretero A, Fernandez-Gutierrez A. 2013. Phenylpropanoids and their metabolites are the major compounds responsible for blood-cell protection against oxidative stress after administration of Lippia citriodora in rats. Phytomedicine, 20:1112-8.

Rasko DA, Sperandio V. 2010. Anti-virulence strategies to combat bacteria-mediated disease. Nat Rev Drug Discov, 9:117-28.

Singh N, Shukla N, Singh P, Sharma R, Rajendran SM, Maurya R, Palit G. 2010. Verbascoside isolated from Tectona grandis mediates gastric protection in rats via inhibiting proton pump activity. Fitoterapia 81:755-761.