Research Article

Boswellia Carteri: A Potential Antibacterial Agent Against common Bacterial Pathogens: In Vitro Study

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ABSTRACT

Boswellia carteri created various physiological effects these are immunomodulatory, anti-inflammatory, anti-cancer and inhibition of human topoisomerases activities. Also; *Boswellia carteri*, showed an important inhibitory activity alongside angiotensin converting enzyme (ACE), neutral endopeptidase and aminopeptidase .

Because of these different and diverse effects then the foundation of the present study was to consider about the antimicrobial activity of *Boswellia carteri* alongside Gram-positive and Gram-negative bacteria regarding the common bacterial infection in diabetic patients.

The bacterial strains used in the study integrated as five Gram-positive bacteria (*Staphylococcus aureus, Streptococcus faecalis, Bacillus cereus, Staphylococcus epidermidis and Staphylococcus saprophyticus*) and three Gram-negative bacteria(*Klebsiella pneumoniae ,Escherichia coli and Pseudomonas aeruginosa*) five for each strains.

The minimum inhibitory concentrations (MIC) of the methanol oil solution were determined for the sensitive bacteria by broth dilution method. Also, Agar-well diffusion method assesses the antibacterial activities which were evaluated by measuring diameters of inhibition zone.

The antibacterial susceptibility of various standard antibiotics against the selected bacteria showed that *Klebsiella pneumoniae* was less susceptible toward most selected antibiotics except amikacine ,while *pseudomonas aeruginosa* showed sensitivity in favor of ciprofloxacin and amikacine but *Escherichia coli* is highly sensitive for standard antibiotics and less sensitive for piperacillin so *boswellia carteri* methanolic solution produced significant antibacterial activity $p<0.05$ in comparison with negative control especially at 80mg/ml against all the involved bacterial strains except *Pseudomonas aeruginosa* which showed higher resistant even at higher concentration of *Boswellia carteri .*

The present study supports the traditional medicinal use of *Boswellia carteri* and suggests that a great consideration should be salaried to this plant which produced significant antibacterial activity against common respiratory bacterial infection.

Keywords: boswellia carteri, antibacterial, in vitro study, respiratory bacterial infection.

INTRODUCTION

The utilize of advanced plants and their provision to treat infectious diseases is an age-old practice and in the past probably the only method available, conversely, the systematic study of higher plants for detecting antimicrobial activity is of reasonably recent origin .These investigations have been triggered by the appearance and spread of antibiotic resistant bacteria causing the effective natural life of existing antibiotics limited ,consequently, the plant kingdom is being screened for newer and efficient chemotherapeutic agents so higher plants can be served both as latent antimicrobial crude drugs as well as a source of new anti-infective agents[1, 2, 3].

Controlled study of plant components follows a logical pathway and preliminary screening of plants for possible antimicrobial activities characteristically begins by using crude aqueous or alcohol extraction and can be followed by a variety of organic extraction methods, because nearly all of the recognized components from plants active in opposition to microorganisms are aromatic or saturated organic compounds, they are often obtained via initial ethanol or methanol extraction[4]. Many of the existing drugs either mimic naturally occurring molecules or have structures that are

entirely or in part derivative from natural plants[5]. Natural antimicrobials can be derived from barks, stems, leaves, flowers and fruits of plants[6]. Although some therapeutic benefits can be traced to specific plant compounds, many herbs contain dozens of active constituent that, collectively, combine to give the plant its therapeutic value. Consequently, it is supposed that the whole plant has more effective healing properties than its selected constituents, and any part of the plant may contain active components[7].

Boswellia carteri scheduled in the USDA Database/Plants Profile as Indian frankincense, which was not measured true frankincense by traditional principles, it produces a soft, odorous resin that hardens in a year; the volatile oils comprise alpha thujene and p-cymene. The resin contains a combination of terpenoids made up of four pentacyclic triterpene acids: ß-boswellic acid, 3-O-acetyl ß (ABA), 11-keto-ß-boswellic acid, and 3-O-acetyl-11-keto-ß-boswellic acid (AKBA). The triterpenoids are the active constituent and are equally called boswellic acids.[8, 9]

Boswellia carteri created various physiological effects these are immunomodulatory activity [10] anti-inflammatory activity[11] anti-cancer[12] inhibitor of human topoisomerases[13]. Moreover, *Boswellia* extracts slow down the renin-angiotensin-aldosterone system and stimulate the kinin system and natriuretic peptides, and so reduce vasoconstriction, increase vasodilation, and improve sodium-water balance[14, 15].
Because of these various and diverse effects therefore the organization of the present study was to think about the antimicrobial activity of *Boswellia carteri* against Gram-positive and Gram-negative bacteria regarding the common bacterial infection.

MATERIALS AND METHODS

This study was carried out in Department of Pharmacology, College of Medicine, Al-mustansiriya University and Department Of Biology, College Of Science, Baghdad University .Baghdad – Iraq, from October to December 2011. It is approved by scientific jury of Department of Pharmacology and licensed by board of medical college.
The bacteria used in the study integrated five Gram-positive bacteria (*Staphylococcus aureus, Streptococcus faecalis, Bacillus cereus, Staphylococcus epidermidis, Staphylococcus saprophyticus*) and three Gram-negative bacteria (*Klebsiella pneumoniae and Escherichia coli and Pseudomonas aeruginosa*) five for each strains. All bacterial cultures were obtained from the Department of Microbiology, college of sciences, Baghdad University.

Agar-well diffusion

Briefly, microorganisms from growth on nutrient agar incubated at 37°C for 18 h were suspended in saline solution 0.85% NaCl and attuned to a turbidity of 0.5 Mac Farland standards (108 cfu/ml). The suspension was used to inoculate 90 mm diameter Petri plates with a sterile non toxic cotton swab on a wooden applicator. Six millimeters diameter wells were punched in the agar and filled with 50 µl of 2000 µg/ml *B. carteri* methanolic solvent. The dissolution of the methanol oil solution was aided by 1% (v/v) DMSO which did, not affect microorganism's growth, according to our control experiments[16]. Commercial antibiotics were used as positive reference standard to determine the sensitivity of the strains and the discs were directly placed onto the bacterial culture and then plates were incubated at 37°C for 24 h. Antibacterial activities were evaluated by measuring inhibition zone diameters.

Broth dilution method

The minimum inhibitory concentrations (MIC) of the methanol oil solution were determined for the sensitive bacteria by broth dilution method. All test extracts were successively diluted from 200 mg/ml to 20, 40, 60, 80 mg/ml. To 9 ml of sterile Mueller-Hinton broth in test tubes, 1 ml of varying concentrations of the extracts were added and then 0.01 ml of the bacterial suspensions which previously adjusted with sterile saline (0.9% w/v) according to 0.5 McFarland turbidity

standard, were introduced to the tubes. Tubes were then incubated at 37^0C for 24 h and after incubation the lowest concentration at which no noticeable growth was experiential was regarded as minimum inhibitory concentration[17, 18].

For each bacterial strain, negative controls were maintained where distilled water (D.W) was used instead of the extract. For positive control, 4 antibiotics, namely Chloramphenicol (30 mcg/disc), Gentamicin (10mcg/disc), Ciprofloxacin (5 mcg/disc) and Imipenem (10 mcg/disc) were used. The experiment was performed two times and the mean values are presented. Drugs Were Obtained From Private Pharmaceutical Company Ltd;luban oil 200mg/ml .

The data analyzed statistically using the unpaired student´s t test, regarding P< 0.05 as significant and expressed as mean ±SD.

RESULTS

The antibacterial susceptibility of various standard antibiotics against the selected bacteria showed that *Klebsiella pneumoniae was less* susceptible toward most selected antibiotics except amikacine ,while *pseudomonas aeruginosa* showed sensitivity in favor of ciprofloxacin and amikacine but *Escherichia coli* is highly sensitive for standard antibiotics and less sensitive for piperacillin table 1.So most of the selected bacterial strains regarded sensitive to the most standard antibiotics.

Table 1: Antibacterial susceptibility testing of various standard antibiotics against bacterial strains

Antibiotics	*Staphylococcus aureus*	*Streptococcus faecalis*	*Bacillus cereus*	Staphylococcus epidermidis	Staphylococcus saprophyticus	*Klebsiella pneumoniae*	*Escherichia coli*	*Pseudomonas aeruginosa*
Ciprofloxacin (5 mcg/disc)	16	2	7	12	13	2	16	6
Gentamicin (10 mcg/disc)	2	11	4	12	0	0	14	0
Piperacillin (100 mcg/disc)	17	11	11	14	16	1	6	0
Chloramphenicol (30 mcg/disc	7	12	14	4	10	0	15	1
Amikacine(30mcg/disc	4	0	12	3	6	12	17	5

Boswellia carteri methanolic solution produced significant antibacterial activity p<0.05 in comparison with negative control especially at 80mg/ml against all the involved bacterial strain except *Pseudomonas aeruginosa* which showed higher resistant even at higher concentration of *Boswellia carteri* table 2.

Table 2: Antibacterial activity of Boswellia carteri methanolic solution

	Zone of Inhibition(mm)			
Bacterial type	20mg/ml	40mg/ml	60mg/ml	80mg/ml
Staphylococcus aureus	9.98	12.66	13.44	15.75
Streptococcus faecalis	9.57	10.37	12.86	13.16
Bacillus cereus	9.87	10.43	12.5	13.88
Staphylococcus epidermidis	10.77	11.65	14.64	15.84
Staphylococcus saprophyticus	9.88	9.89	10.64	11.89
Klebsiella pneumoniae	11.76	13.65	15.43	17.42
Escherichia coli	10.6	11.8	12.7	14.2
Pseudomonas aeruginosa	0.0	2.1	2.2	2.2

Minimal inhibitory concentration (MIC) of *Boswellia carteri* methanolic solution was better against *Klebsiella pneumonia* 6±0.22(mg/ml) and less effective against *Pseudomonas aeruginosa*32±3.25 (mg/ml) but moderated against other bacteria table(3).

Table 3: Minimal inhibitory concentration (MIC) of *Boswellia carteri* methanolic solution

Bacterial type	MIC (mg/ml)
Staphylococcus aureus	**11±2.11**
Streptococcus faecalis	**12±2.21**
Bacillus cereus	**14±3.12**
Staphylococcus epidermidis	**14±2.32**
Staphylococcus saprophyticus	**15±2.11**
Klebsiella pneumoniae	**6±0.22**
Pseudomonas aeruginosa	**32±3.25**
Escherichia coli	**12±2.11**

DISCUSSION

In this study *Boswellia carteri* created significant antibacterial againsts Gram-positive and Gram-negative bacteria that evaluated by Agar-well diffusion and Broth dilution methods.

Through exclusion toward *Pseudomonas aeruginosa*, the lack of susceptibility of *Pseudomonas aeruginosa* toward *Boswellia carteri* could be accredited to the dependability that this bacteria is clearly resistant to many antibiotics due to the permeability barrier afforded by its outer membrane. Moreover; *Pseudomonas aeruginosa* tend to colonize in a biofilm form which makes these bacteria self-protective to therapeutic concentrations of most antibiotics. Within view of the fact that its ordinary habitat is the soil, living in connection with bacilli, actinomycetes and molds, it has developed resistance to a variety of their naturally occurring antibiotics[19].

The active constitutive ingredients of *Boswellia carteri* resins explained by Anthoni 2006 *et al* study which reported that ethanolic extract of *Boswellia carteri* resin comprises 7 boswellic acids[20]. Akihisa et al 2006 study showed that methanolic extract of *Boswellia carteri* resin consists of 15 triterpene acids, including boswellic acids, and 2 cembrane-type diterpenes [21]. 11-ketoboswellic acid, the strongest anti-inflammatory component of the resin, selectively blocks leukotriene biosynthesis through inhibiting 5-lipoxygenase activity in rat neutrophilic granulocytes and provides protective effects in a chemically induced mouse ulcerative colitis model[22].

In adding, boswellic acids have been shown to acquire anti-cancer actions through their cytostatic and apoptotic properties in multiple human cancer cell lines[23,24].

In this interpretation, we established that a commercial source of *Boswellia carteri* oil fashioned antimicrobial effects regardless of its wide spectrum actions on different organ functions.

The mechanism of antibacterial activity of *Boswellia carteri* is connected to its chemical constituents.

Boswellic acid have also been reported to be safe and be appropriate minimal toxicity on human skin cells[25, 26]. The chief chemical components of *Boswellia carteri* resins can be separated into three groups:Volatile oils or lower terpenoids, higher terpenoids, and carbohydrates. The higher terpenoids comprises of b-boswellic acids as the main triterpenic acid along with 11-keto-b-boswellic acids and their acetates[27].

The boswellic acids are organic acids, consisting of a pentacyclic triterpene, a carboxyl group and at slightest one other functional group. Alpha-boswellic acid and beta-boswellic acid, both have an

additional hydroxyl group; they differ only in their triterpene structure. Acetyl-alpha-boswellic acid and acetyl-beta-boswellic acid, replace the hydroxyl group with an acetyl group. Other boswellic acids include the keto-boswellic acids and their acetyl counterparts[28].

Weckessera *et al* 2007 study reported that the antibacterial activity of *Boswellia* dry extracts is efficient against aerobic and anaerobic bacteria such as *Streptococcus, Corynebacteria, C. perfringens and P. acnes*.[29]

The increased uptake of propidium iodide(Propidium iodide is fluorescent nucleic acid stain that binds to DNA by intercalating between the bases with little or no sequence preferred) in the keto-ß-boswellic acid treated cells of *S aureus* indicated that keto-ß-boswellic acid distorted the cell membrane structure, ensuing in the disruption of the permeability barrier of microbial membrane structures and escape of cytosolic constituent from *S. aureus* cells in the attendance keto-ß-boswellic acid over an era of two hours was appreciably higher than background levels. These clarifications point out that the antimicrobial activity of keto-ß-boswellic acid consequences from its ability to interrupt the permeability barrier of microbial membrane structures.[30] The lack of antibacterial activity of AKBA against Gram-negative bacteria may be attributed due to the presence of lipophilic outer membrane and this external layer of the Gram-negative outer membrane is collected primarily of lipopolysaccharide molecules and forms a hydrophilic permeability barrier as long as shield against the effects of highly hydrophobic compounds[31].

This may be the potential explanation of the resistance of Gram-negative bacteria to lipophilic keto-ß-boswellic acid. In our study analogous observations have been made in other studies also, where lipohilic terpenes such as thymol, eugenol, and bakuchiol have reported low sensitivities against Gram-negative bacteria[32, 33].

Terpenes are a large and varied category of organic compounds, formed by a variety of plants, essentially conifers, Terpenoids are also known as isoprenoids. Diterpenes are composed of four isoprene units and have the molecular formula $C_{20}H_{32}$. They obtain from geranylgeranyl pyrophosphate. Examples of diterpenes are cafestol, kahweol, cembrene and taxadiene[34,35].

Terpenes and Diterpenes of *Boswellia carteri* produced their antimicrobial activity via different mechanisms, may act by iron deprivation, hydrogen bounding or non specific interactions with essential proteins such as enzymes [(36)]. Sawer et al. 2005 study established that Diterpenes alkaloid and cryptolepine, causes cell lysis and morphological changes of *S. aureus*[37].

Moreover; Guittat *etal* 2003 and Banno *et al* 2006 studies showed that oxygenated monoterpenes were reported to be responsible for the antimicrobial activity of several essential oils. Accordingly, the high antibacterial value of *Boswellia carteri* could be attributed to the high percentage of oxygenated monoterpenes such as camphor and a-fenchol, in addition, the predominance of 2-hydroxy-5-methoxy-acetophenone (16.3%) could probably contribute to the experiential strong antibacterial activity but the antimicrobial property of the *Boswellia carteri* may be through a diverse mechanism, since the compound is known to be a DNA intercalator and an inhibitor of DNA synthesis through topoisomerase inhibition[38,39].

Furthermore *Boswellia carteri* slow down bacterial type II Topoisomerases enzymes and virtually every eubacteria encodes two type of type II topoisomerases; gyrase and topoisomerase IV. [(40)] Gyrase is the only familiar type II enzyme that is double helix and concerned mainly in adaptable the superhelical density of DNA and alleviating torsional stress of DNA tracking systems also gyrase and topoisomerase IV are targets for quinolone-based antibacterial drugs such as ofloxacin and ciprofloxacin, which are among the majority active and broad spectrum antibacterial agents currently in clinical use[41].

As well *Boswellia carteri* bind human type II Topoisomerases and several topoisomerase II poisons are in wide clinical use as successful chemotherapeutic drugs like amsacrine,

daunorubicin, doxorubicin, and etoposide so *Boswellia carteri* efficient in the treatment of a number of malignancies by means of inhibition of the DNA strand in the topoisomerase II cleavage complex, leading to double strand breaks, which can lead to the production of chromosomal aberrations, weaken the genome, and trigger cell death pathways[42].

So our study showed that *Boswellia carteri* produced significant antibacterial activity similar to that of quinolone regarding the relative similarity in the results of bacterial sensitivity of *Boswellia carteri* and ciprofloxacine, also *Boswellia carteri* modulate the respiratory inflammation via blocking lipooxygenase enzyme so decrease leukotriene level and for this two important actions *Boswellia carteri* regarded as standard therapeutic agent for common respiratory bacterial infections.

CONCLUSIONS

The results of the present study support the traditional medicinal use of *Boswellia carteri* and suggest that a great consideration should be salaried to this plant which is found to have many pharmacological properties and produced significant antibacterial activity against common infection.

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