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POTENTIAL USE OF *CARIUM CARVI* AND *CURCUMA LONGA* FOR THE REMEDY OF SKIN AND SOFT TISSUES PATHOGENS

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ABSTRACT

The Pathogens responsible for the skin and soft tissue infections are often prone to develop resistance to antibiotics. A good alternative to this resistance is the use of folk medicine. For this purpose two plants *Carium carvi* and *Curcuma longa***,** used in folk medicine were tested against the selected pathogens, *Staphylococcus aureus*, *Staphylococcus epidermidis, Pseudomonas aerugenosa* and *Streptococcus pyogenes.* The pathogenswere collected from the patients having skin and soft tissues infections. The isolated pathogens were identified through microscopic studies followed by biological tests using Sigma Aldrich KGaA Merck kit protocol. These plant materials were extracted with MeOH and then portioned among different solvents, based on their polarity. These extracts were then applied against the selected pathogens, using well diffusion assay method and the minimum inhibitory concentration (MIC). The results showed marked antibacterial activity in the chloroform and ethyl acetate extract (18 mm zone of inhibition each) of *Carium carvi* seeds while the chloroform extract of *Curcuma longa* showed (21 mm zone of inhibition) promising results. Sensitivity of various extracts of the plant in a concentration dependent manner with significant MIC values was determined. Our findings showed that the extracts of *C. longa* and *C. carvi* seeds possess strong antibacterial effects against clinically isolated skin and soft tissue pathogens.

Keywords: *Carium carvi*, *Curcuma longa,* Skin diseases, Pathogens, Antibacterial activity.

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INTRODUCTION

Skin diseases are producing a high health concern both in developed and developing countries, in all ages from children to the old people and are one of the five causes for medical deliberation. A basic problem associated with these skin disease causing pathogens is the creation of resistance. The antibiotic resistance is on the rise in the whole world at an alarming rate which is threatening the human ability to treat even some common diseases successfully. Only in the United states of America, the methicillin resistant *Staphylococcus aurens* (MRSA) has affected nearly 126,000 people and causes 1860 deaths every year. This number is more than the deaths caused by AIDS (Quave *et al*., 2012). As the skin disease are more in the poor population in the remote areas of Asia and Africa where the health care and the modern health facilities are in scarcity. Therefore these people are a lot dependent upon the natural remedies. In this situation the natural products are the best source of drugs and drug leads, and this is still true despite the enormous development in the synthetic drugs. The natural product poses unique structural and chemical diversity that is unparallel by the synthetic world. In this situation the folk resources of medicinal origin for control of antibiotic resistant pathogenic bacteria is increasing with every passing day due to the increasing side effects of the synthetic drug (Khan *et al*., 2015; Khan *et al*., 2016). Medicinalplants have been an effective source of widely acceptable and efficient medicines because of the popular assumption that the herbal medicines cause fewer or no side effect and are effective agents against a broad range of antibiotic resistant microorganisms (Bashir *et al*., 2014). *C. carvi* and *Curcuma longa* are the two plants used in northern areas of Pakistan for the cure of skin related diseases.

Carium carvi (Zankay) belongs to family Apiaceae is the oldest herbs, having a pleasant smell, found in Africa, Asia and Europe. Its fruits are used in medicine, fragrance and for cooking purposes. *C. carvi* consist of important nutrients such as vitamin A, B complex, vitamin C and E. The desiccated fruits of *C. carvi* are used in medicine as a flatulence carminative, they are helpful against spasmodic, gastrointestinal complaint, irritable stomach, dyspepsia, lack of hunger in adult (Sibi *et al*., 2013). *C. carvi* oil has antimicrobial, antifungal, molluscidal, nematicidal, anti oxidant and anti carcinogenic (Satish *et al*., 2008; Jain *et al*., 2010; Abhilash *et al*., 2011). It's extract posses *in vitro* antibacterial activity against *H. pylori*, the alcoholic extract of *C. carvi* inhibit the growth of *Klebsiella pneumonia.* Antifungal activity of *C. carvi* is recorded

against animal, food and soil fungi such as dermatophyte, mycotoxin and yeast.(Razzaghi-Abyaneh *et al*., 2009). The seed of *C. carvi* is used in the healing of bronchitis and is an element of cough remedy, especially valuable for children and mothers for enhancement of breast milk (Chevallier, 2001). It is used to improve liver functions and as a remedy for headache, when mixed with castor oil is used for scabies (Sivarajan and Balachandran, 1994). The *C. carvi* essential oils have also been used as an anti ulcerogenic, antitumor, antiproliferative and antihyperglycemic agent (Thippeswamy *et al*., 2013).

Curcuma longa (Family: Zingiberaceae), is an evergreen herbaceous plant grown widely in the sub-continent, Africa, China, India and some countries of South America. The use of *Curcuma longa* has raised due to its coloring property and pleasant odor in food (Amin, 1991). The phenolic compounds, curcuminoid dyes and essential oils are responsible for the antioxidant activity of turmeric plant (Nafissi, 1990). Phenolic compounds of *Curcuma longa* exhibits the potential to destroy cell walls of target bacteria and enter into the microbial cell and affect the metabolism of the cell (Končić *et al*., 2010). The anti-protozoal, anti-venom, anti-HIV, anti-tumor activities have also been reported of the *Curcuma longa* (Shamsa *et al*., 1999; Turkmen *et al*., 2006; Arayne *et al*., 2007; Farhoosh *et al*., 2007). *Curcuma longa* consists of curcumin used for antimicrobial skin gels and for wound covering properties (Zhou *et al*., 2009). Curcumin also possesses inhibitory activity against methicillin-resistant *Staph. aureus (Kong et al., 2009).* Curcumin activates Inosine monophosphate dehydrogenase (IMPDH) enzyme which can inhibit guanine nucleotide synthesis and is suggested as a antiviral and anticancer drug (Kumar *et al*., 2010). Curcumin inhibit viral long terminal repeat (LTR) and a consequent can inhibit type 1 human immunodeficiency virus (HIV-1) virus transcription. Methanolic extract of *Curcuma longa* show antifungal activity against *Candida albicans* and *Cryptococcus neoformans* (Raghavendra *et al*., 2006). As an anti-inflammatory substance having a liver protective effect has also been reported. The anti-allergy, insect-repellant and anti-ulcer activities are additionally reported (Babu *et al*., 2007).

In the present study different solvent extracts of *C. carvi* and *C. longa,* the plants which are used indigenously for skin cure, against clinically isolated skin pathogens including *P.aerugenosa*, *S.aureus*, *S.epidermidis* and *S.pyogenes* were investigated.

Experimental

Study Area and Sampling: The sample of plants *C. carvi* and *C. longa* were collected from District Khar. The plant material was identified by plant taxonomist from the Department of Botany, and was given the voucher specimen no KUST 424 deposited in the herbarium of Kohat University of Science and Technology (KUST).

ExtractionandFractionation: Chopped the one kilogram dried plant samples into pieces and then grinded into powder. The powder materials of the plants were dipped in methyl alcohol with occasional shaking for 12 days at room temperature in the laboratory of the Department of Chemistry, Kohat University of Science & Technology (KUST). The solvent was filtered after every 4 days and the filtrate was concentrated using vacuum rotary evaporator at 42 ^{0}C. The plant powder was again dipped in methanol and repeated the above mentioned process three times. At the end combined all the filtrates and concentrated till dryness and then dissolved in distilled water. This water solution was then extracted with n-hexane, chloroform and ethyl acetate in succession to get the extracts of n-hexane, chloroform and ethyl acetate.

Collection and Identification of Bacteria: Bacterial samples were collected from Hayatabad Medical Complex (HMC) and North West General Hospital (NWGH) Peshawar, Khyber Pakhtunkhwa in Nutrient broth tubes. The patients consent was sorted for the collection of samples and further work. These cultured bacteria namely *P. aerugenosa*, *S. aureus*, *S. epidermidis* and *S. pyogenes* were stained with Gram's stain and subjected to microscopic observation for the identification of their cell morphology. The results based on microscopic observation were further confirmed using biochemical tests. For this purpose the Catalase, Coagulase, DNase and Oxidase tests were performed as per Sigma Aldrich KGaA Merck kit protocol 2010. The results are given in Table 1.

Culture Meida: Mac Conkey and Blood agar was used to culture the bacteria. Both have different characteristics. Mac Conkey agar is a differential media for Gram Negative Bacteria. Blood agar acts as an enriched media facilitating the growth of Gram Positive Bacteria and differentiates Bacteria on the basis of heamolysis of blood.

Bacteria Culture: The bacteria strains were cultured on Nutrient agar and Muller Hinton agar (MHA) media. Nutrient agar media enhances the growth of bacteria while the MHA was used for susceptibility testing of the selected bacteria against the plant extracts and antibiotics. The bacteria culture was refreshed in nutrient broth for 24 h at 37°C before inoculation of bacteria (Ahmad and Aqil, 2007).

Bacterial Susceptibility Testing: Well diffusion assay and minimum inhibitory concentration (MIC) methods were used for the determination of antibacterial potential of different fractions of the plant extracts. For the assay four strains of skin bacterial pathogens namely, *P. aerugenosa*, *S. auerus*, *S. epidermidis* and *S. pyogenes*

were used. The Mueller Hinton agar (Oxide, UK) media was prepared in a conical flask according to the manufacturer directions. After preparation of media in the flask, the media was poured in the plates. After the media was solidified in plates, inoculated fresh culture of the strain (adjusted to 0,5 McFarland turbidity) on each plate by means of spreader. Seven wells (6mm diameter each) were made through cork borer in the plates and then added 100 µl of the plant extract through micropipette. Used dimethylsulfoxide (DMSO) as negative control, while the Impenim (Standard antibiotic) as positive control. Labeled the plates and placed in incubator for 24 hrs at 37°C for aerobic incubation. Zone of inhibition was measured by a scale in millimeter (Coyle, 2005). The results of antibacterial activity of extracts of *Carum carvi* and*Curcuma longa,* against skin pathogens are shown in Table 2 and 3.

Minimum Inhibitory Concentrations (MICs): The plant extracts were checked for their qualitative antibacterial activity against the selected pathogens through MIC method. Took 10 ml nutrient broth in a 15 ml sterilized, caped tube and then inoculated with 100 µl of overnight bacterial broth cultures, matched to 0.5 McFarland standards (Kumar *et al*., 2010).).The only nutrient broth was taken as negative control while the positive control was nutrient broth having bacterial culture. The tubes were then incubated at 37 °C for 24 h and recorded the results (Coyle, 2005). The MIC values of various extracts of the plants are given in Table 4

Phytochemical Analysis: The active metabolites of the plants like glycosides, steroids, tannins, terpenoids, alkaloids, flavonoids amino acids saponin were determined qualitatively (Bladt, 2009). Crude extract of *C. carvi* consist of carbohydrate in high concentration, alkaloid, phenol, tannins and starch were in moderate concentration while glycoside, saponin, flavonoid and protein were not found while in *C. longa* the carbohydrate was in high concentration, the alkaloid, glycoside, tannins were in moderate concentration while, saponin, flavonoid, starch and phenol were not found as shown in Table 5.

Statistical Analysis All the experiments for determining the zone of inhibition were performed in triplicate, mean zone of inhibition and standard deviation were calculated. The results were expressed as mean ± standard deviation. Statistical analysis was done by one way ANOVA. The statistical significant value was set at $p< 0.05$.

RESULTS AND DISCUSSION

The antibiotic resistance is on the rise in the whole world at an alarming rate which is threatening the human ability to treat even some common diseases successfully (Loke and Hanafi, 2019). In this situation the natural products are the best source of drugs and drug leads, and this still true despite the enormous development in the synthetic drugs. The natural product poses unique structural and chemical diversity that is unparallel by the synthetic world. In this situation the folk resources of medicinal origin for control of antibiotic resistant pathogenic bacteria is increasing with every passing day due to the increasing side effects of the synthetic drug (Ullah *et al*., 2013; Khan *et al*., 2015). Plants have been an effective source of natural and efficient medicines because it is assumed that plant based medicines cause fewer or no side effect and influence a broad range of antibiotic resistant microorganisms (Bashir *et al*., 2014). Two local medicinal plants *Carum carvi* and*Curcuma longa* were checked for the activities against skin and soft tissues pathogens. Methicillin-resistant *S. aureus* (MRSA) is widely recognized as a nosocomial pathogen in health related zones. It is now emerging as a prominent cause of community acquired infections across the world and also reported in healthy individuals without risk factors (Iyer and Jones, 2004; Fleming *et al*., 2006). The results of our finding showed prominent susceptibility of various extracts of *C. carvi* seeds and *C. longa* against clinically isolated *S. aureus*. *S. epidermidis* has been recognized as an opportunistic human pathogen and a pre-dominant cause of nosocomial infections in recent years. Its pathogenicity is primarily attributed to the ability to form biofilms on indwelling medical devices. *Staphylococcus epidermidis* is protected in a biofilm, against attacks from the immune system and against antibiotic treatment, making *S. epidermidis* infections difficult to eradicate (Vuong and Otto, 2002). When we tested the extracts of *C. carvi* seed and *C. longa* against clinically isolated *S. epidermidis,* marked antibacterial effect was observed. It is, therefore, strongly recommended to lunch further detail studies to investigate its effect followed by bioactivity guided isolation of secondary metabolites for better understanding and clinical significance.

Emerging antibiotic resistance of *S. pyogenes* (erythromycin resistance) is alarming, because it is one of the common causes of a variety of skin and soft-tissue infections and because empirical choices of antimicrobials must include agents with activity against resistant strains (Stevens *et al*., 2014). Minor skin and soft-tissue infections may be empirically treated with commonly used antibiotics, but resistance cases will be difficult to treat. Based on the results of our study on the extracts of *C. carvi* seed and *C. longa*, it could be a useful natural alternative to current synthetic agents. *P. aeruginosa*is an important causative agent of skin and soft tissues nosocomial infections, particularly in patients with compromised host defense mechanisms. It is the most common pathogen isolated from patients who have been hospitalized longer than one week. If not properly treated, such infections can be life-threatening. Multiple

drug resistant has been frequently reported to *P. aeruginosa* infections in literature (Paterson, 2006). The extracts of *C. carvi* seed and *C. longa* showed promising result against clinically isolated *P. aeruginosa.* The study shows that mostly the chloroform and ethyl acetate extracts has shown good activity while in some cases the hexane extract has performed better, this indicate that the non polar or less polar compounds like terpenes, alkaloids and tannins might be the active ingredients of the plant extracts. As the extracts of *C. carvi* seed and *C. longa* showed promising result against these pathogens, thus the extracts of these plants could be a useful alternative to current available therapies.

Table 1. The biochemical tests for the identification of bacteria.

S.No	Bacteria	Biochemical Tests
1	*Staphylococcus aureus*	Catalase +ve , Coagulase +ve, DNase test +ve,
2	*Staphylococcus epidermidis*	Catalase +ve, Coagulase -ve, Dnas test –ve, Oxidase –ve.
3	*Streptococcus pyogenes*	Catalase –ve, Coagulase –ve, DNase –ve,
4	*Pseudomonas aerugonosa*	Oxidase +ve, Catalase +ve. Coagulase –ve.

Table 2. Antibacterial activity of extracts of *Carium carvi* seed against skin pathogens.

Extracts	Concentration	Zone of inhibition (mm)			
		Staphylococcu aureus	***Streptococcus pyogenes***	***Staphylococcus epidermidis***	***Pseudomonas aerugenosa***
Positive control		26.000±1.6	33.33±1.6	31.889±1.6	27.778±1.1
Hexane	12.5mg/ml	1.000±0.9	1.667±1.2	1.667±0.8	2.333±1.5
	25mg/ml	10.333±1.0	11.667±0.5	11.000±1.0	12.333±0.1
	50mg/ml	18.000±0.8	16.667±1.2	18.333±1.2	15.333±1.5
Chloroform	12.5mg/ml	3.000± 0.8	1.667±1.2	1.667±1.2	1.667±0.9
	25mg/ml	11.333±1.2	12.000±1.8	9.000±1.2	10.667±1.5
	50mg/ml	15.667±1.5	16.667±1.6	18.000±1.5	17.333±1.5
Ethyl acetate	12.5mg/ml	1.667±0.9	2.667±1.2	2.000±1.2	1.667±0.4
	25mg/ml	12.000±1.6	14.000±1.8	13.33±1.6	12.333±1.8
	50mg/ml	17.667±1.5	18.333±1.8	17.000±1.8	14.667±1.2
Aqueous	12.5mg/ml	1.000±0.2	1.667±0.5	1.667±0.8	1.667±0.5
	25mg/ml	8.000±1.6	6.333±1.2	10.667±1.6	10.000±1.2
	50mg/ml	12.333±1.6	16.333±1.2	13.000±1.8	15.333±1.2
DMSO		0.000	0.000	0.000	0.000

Values are mean ± SEM of three independent experiments. **. DMSO: Dimethyle Sulfoxide**

Table 3. Antibacterial activity of extracts of *Curcuma longa* seed against skin pathogens.

Extracts	Concentration	Zone of inhibition (mm)			
		Staphylococcu aureus	***Streptococcus pyogenes***	***Staphylococcus epidermidis***	***Pseudomonas aerugenosa***
Positive control		27.444±1.7	30.667±0.9	29.889±2	29.556±2
Hexane	12.5mg/ml	3.000±0.2	1.667±0.2	2.000± 0.5	0.667±0.5
	25mg/ml	12.333±1.6	7.333±1.6	11.000±1.2	11.333±1.2
	50mg/ml	18.667±1.6	15.333±2	17.667±2	18.000±1.8
Chloroform	12.5mg/ml	1.000±0.4	1.000±0.9	1.667±0.6	1.667±0.2
	25mg/ml	3.667±1.2	6.000±0.8	10.000±1.5	9.667±1.2
	50mg/ml	21.000±0.9	16.667±1.5	17.667±1.6	18.333±2
Ethyl acetate	12.5mg/ml	3.000±0.2	2.000±0.4	3.000±0.5	1.667±0.2
	25mg/ml	7.000±1.7	7.000±1.6	8.667±1.9	9.667±1.6
	50mg/ml	16.333±1.7	18.000±1.6	15.000±1.5	18.000±1
Aqueous	12.5mg/ml	1.333±0.5	1.000±0.4	1.667±0.2	1.667±0.2
	25mg/ml	7.333±	12.333±	11.667±	5.000±
	50mg/ml	15.667±	15.000±	15.667±	17.667±
DMSO		0.000	0.000	0.000	0.000

Values are mean ± SEM of three independent experiments.

Table 4. Minimum inhibitory concentrations (MIC) of plant *Carium carvi* crude extract against skin pathogens.

Extracts	Bacteria isolates	MIC (mg/ml)
Hexane	*Staphylococcu aureus*	25.25
	Streptococcus pyogenes	50.25
	Staphylococcus epidermidis	25.25
	Pseudomonas aerugenosa	65.25
Chloroform	*Staphylococcu aureus*	27.25
	Streptococcus pyogenes	40.00
	Staphylococcus epidermidis	25.25
	Pseudomonas aerugenosa	35.50
Ethylacetate	*Staphylococcu aureus*	25.50
	Streptococcus pyogenes	25.50
	Staphylococcus epidermidis	50.25
	Pseudomonas aerugenosa	75.50
Aqueous	*Staphylococcu aureus*	110.50
	Streptococcus pyogenes	56.50
	Staphylococcus epidermidis	125.50
	Pseudomonas aerugenosa	150.50

Table 5. Phytochemical analysis of *Carium carvi* seeds and *Curcuma longa.*

Plants	Phytochemical tests								
	Alkaloid	Carbohydrate	Glycoside	Saponin	Phenol	Tannins	Flavinoid	Protein	Starch
Carium carvi Seeds	++	+++	-	-	++	++	-	-	++
Curcuma longa	+	+++	++	-	-	++	-	+	-

- sign shows not detected; + shows compound present in small amount; ++ shows compound present in moderate amount; +++ shows compound present in higher amount.

Conclusion: The extracts of *C. carvi* seed and *C. longa* showed promising results against clinically isolated skin related *Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aerugenosa* and*Streptococcus pyogenes* pathogens. Therefore, it can be concluded that its extracts/isolated compounds could be useful natural alternative against these pathogens.

Ethical consideration: The work has been approved by the KUST Ethical Committee wide approval No. KUST/ Ethical Committee /16-05.

Declarations:

Competing interests: The authors declare that they have no competing interests.

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