RESEARCH ARTICLE

DEVELOPMENT OF NOVEL TOPICAL COSMECEUTICAL FORMULATIONS WITH ANTIMICROBIAL ACTIVITY AGAINST ACNE-CAUSING MICROORGANISMS FROM *Coriandrum sativum* L.

Nirmani Wishwakala Nawarathne[1], Kanchana Wijesekera[1], Gaya Bandara Wijayaratne[2], Mayuri Napagoda[3]*

[1]Department of Pharmacy, Faculty of Allied Health Sciences, University of Ruhuna, Galle 80000, Sri Lanka, [2]Department of Microbiology, Faculty of Medicine, University of Ruhuna, Galle 80000, Sri Lanka, [3]Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle 80000, Sri Lanka

ABSTRACT

Spices possess a diverse array of natural phytochemicals with antibacterial, anti-inflammatory, and antioxidant effects. Hence spices could be employed to treat chronic dermatologic conditions like acne vulgaris which involves infection of *Propionibacterium acnes* and *Staphylococcus aureus*, and inflammation. Particularly with the emergence of antibiotic resistance, there is an utmost necessity for the development of novel therapeutic agents for the management of acne. Thus, this study was focused on the development of novel topical gel formulations from the seeds of *Coriandrum sativum* L. (coriander) and to evaluate the antibacterial potential against some acne-causing bacterial species. Initially, the antibacterial effects of the *n*-hexane, ethyl acetate, and methanol extracts were screened against *S. aureus* and *P. acnes* by agar well diffusion assay. Thereafter, ethyl acetate extract of *C. sativum* was incorporated at predetermined three different concentrations into a novel topical gel base. Agar well diffusion assay and the broth microdilution method were used to evaluate the antibacterial activity of the resulting formulations. Interestingly, all three formulations inhibited the growth of *P. acnes* and *S. aureus*, with the highest activity in the formulation comprised of 15% w/w of the seed extract. Furthermore, the antibacterial activity and physical parameters like pH, color, and consistency of these formulations were retained during the storage period of 30 days, demonstrating their suitability as effective therapeutic alternatives in the management of acne vulgaris.

Keywords: *Acne vulgaris, Coriandrum sativum* L., *Propionibacterium acnes, Staphylococcus aureus*

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*Corresponding author: *mayurinapagoda@yahoo.com*

1. INTRODUCTION

A spice is described as 'any dried, aromatic and pungent plant substance which is employed as the whole or ground form and utilized mainly as flavor enhancers, colorants fragrants and preservatives in food' [1]. Beyond their common utility as flavor enhancers and coloring agents, spices are employed as highly potent antiseptics owing to their antimicrobial activities. Further, the latest scientific investigations revealed that culinary herbs and spices possess a diverse array of bioactive phytochemicals that are potentially involved in their therapeutic effects [2]. Among the spices, *Coriandrum sativum* L. (coriander) is well-recognized due to its bactericidal, analgesic, anti-inflammatory, antioxidant, and fungicidal activities. The presence of polyphenolic compounds in almost all spices including *C. sativum* could reinforce their suitability as remedies for several dermatologic clinical conditions like acne vulgaris [3,4].

Acne vulgaris is considered the most abundant dermatologic condition which affects late adolescents throughout the globe and the data of the Global Burden of Disease (GBD) study revealed that it affects nearly 85% of young adults in the age group of 12–25 years [5]. Acne is generally characterized by the presence of follicular hyperkeratinization, seborrhea, microbial colonization, and inflammation. Thus, acne is mainly treated with chronic use of antibiotics and in some severe cases with isotretinoin. However, the emergence of antimicrobial resistance along with detrimental adverse effects such as hepatic dysfunction, and teratogenic effects associated with currently available therapeutic agents demand the search for novel anti-acne agents with low side-effect profiles [6]. Therefore, the interest in the usage of natural and herbal preparations to replace conventional therapies becomes heightened. Moreover, the enthusiasm of the general public toward green medicine influences the quality research on plant-based formulations to alleviate the sufferings of acne-victimized patients [7]. Consequently, the formulation and use of anti-acne products, particularly gels of herbal origin received more attention recently [8].

According to the literature, anti-acne formulations including gels, have been developed from herbal materials enriched with antibacterial, anti-inflammatory, and antioxidant constituents; for example, *Garcinia mangostana* and *Aloe vera* [9–12]. In this respect, employing natural ingredients like the seeds of *C. sativum* in the form of cosmeceuticals,

instead of synthetic therapeutic agents could be anticipative in the management of acne flares as it is a well-established fact that the seeds of coriander are fortified with natural antioxidants, antibacterial and anti-inflammatory compounds [13,14]. Therefore, the present investigation has focused on the development of topical cosmeceutical formulations incorporating *C. sativum*, a spice widely employed in folklore medicine in Sri Lanka as an anti-infectious and anti-inflammatory remedy [15], and the evaluation of the antibacterial activity of the prepared formulations against selected acne-causing bacteria.

2. MATERIAL AND METHODS

2.1 Plant materials

The seeds of *C. sativum* were purchased and authenticated from a government-registered Ayurvedic chemical laboratory (registered number-Ayur/Nish/Put/09) in Chilaw, North Western Province, Sri Lanka. A voucher specimen (MN_2018_005) was deposited at the Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Sri Lanka for future reference. Dried seeds (20 g) were initially soaked in approximately 400 mL of *n*-hexane, ethyl acetate, and methanol solvents (Sigma-Aldrich) separately for 24 hours in a shaker. Thereafter the solvents were evaporated using a rotary evaporator (HAHNVAPOR, HS-2005V). These crude extracts were subjected to antimicrobial activity assays against *S. aureus* to identify the best solvent for a large-scale extraction procedure.

2.2 Preliminary screening of crude extracts for antibacterial activity against S. aureus

The antibacterial activity against *S. aureus* was determined by the agar well diffusion assay following the method initially described by Valgas et al. [16] and modified by Nawarathne et al. [8]. *S. aureus* (ATCC 25923) was obtained from the Department of Microbiology, Faculty of Medicine, University of Ruhuna, Sri Lanka. Mueller Hinton Agar (MHA) (Oxoid) plates were inoculated with a saline suspension of bacteria (matched with the turbidity of McFarland 0.5 standard) prepared using isolated colonies of one-day-old pure cultures of *S. aureus*. The wells (diameter-6 mm, depth-5 mm) were prepared at equidistance in MHA plates using a sterilized cork borer. The wells were filled with 50µL of each of the test solutions of 20 mg/mL concentration of hexane, ethyl acetate, and methanol extracts dissolved in 2% DMSO separately. Thereafter the plates were incubated

at 37 °C overnight and the diameter of the zones of inhibition around each well was measured by millimeter scale. Co-amoxiclav (GSK) was used as the positive control while 2% DMSO and methanol were used as the negative controls. The zones more than 6 mm were considered inhibitions resulting from the significant antibacterial activity. The experiment was performed in duplicate and the diameter of the zone of inhibition was expressed as mean ± SD. Depending on the diameter of the zones of inhibition, the best solvent for the large-scale extraction was selected.

2.3 Large-scale extraction of the seeds of C. sativum

Considering the results obtained from the preliminary antibacterial screening tests against *S. aureus*, ethyl acetate was selected as the solvent for the large-scale extraction of the seeds of *C. sativum.* Dried seed materials (500 g) were extracted with ethyl acetate (2.5 L) solvent for 24 hours under shaking and thereafter the solvent was evaporated at 38 ºC using the rotary evaporator. Then the extract was incorporated into the gel base consisting of carbapol (Sigma-Aldrich), cetyl alcohol (Sigma-Aldrich), triethanolamine (Sigma-Aldrich), and rose water to obtain topical gel formulations.

2.4 Preparation of topical gel formulations

Three topical gel formulations were prepared by incorporating the ethyl acetate extract of the seeds of *C. sativum* at predetermined concentrations of 5% w/w (formulation F1), 10% w/w (formulation F2), and 15% w/w (formulation F3). The antibacterial activity of the extract at these concentrations was evaluated by agar well diffusion method against *S. aureus* (as mentioned earlier) and *P. acnes* under anaerobic conditions, against erythromycin (GSK) as the positive control prior to the preparation of the gel formulations. This experiment was conducted to ensure that the incorporation above concentrations of ethyl acetate extract would offer an antibacterial effect to the resulting products.

In the formulation, carbapol 940 was used as the gelling agent as it is proved to be an inert carrier to earn the controlled release behavior of active phytochemicals in a gel formulation, and particularly it possesses a microgel structure which is more favorable to exert its therapeutic action. Triethnolamine was used as a neutralizing agent to counterbalance the anionic carbapol and to obtain the required consistency [17]. In the process of formulating the gel products, glycerin (Sigma-Aldrich), phenoxy ethanol

(Sigma-Aldrich), EDTA (Sigma-Aldrich), rose water, cetyl alcohol, fuller's earth, polyethylene glycol (Sigma-Aldrich), and triethanolamine were incorporated together [12,14]. Carbapol 940 was dissolved in rose water and the carbapol mixture was kept overnight at 40 °C until it got soaked completely. Thereafter, glycerin, phenoxy ethanol, EDTA, rose water, cetyl alcohol, fuller's earth, and polyethylene glycol were added to this carbapol mixture while stirring in a vortex. This was followed by the addition of triethanolamine with continuous stirring until appropriate consistency was obtained and subsequently, the seed extract was incorporated into the prepared gel base at varying percentages.

2.5 Antibacterial activity studies for the gel formulations

All three topical gel formulations were solubilized in methanol for the antimicrobial assays against *S. aureus* and *P. acnes*. The gel base and methanol were used as the negative controls while a synthetic commercial anti-acne gel was used as the positive control in these experiments.

The antibacterial effect of the gel formulations against *S. aureus* was determined by the agar well diffusion method following the method described above. The broth microdilution method described by Eldeen and Van Staden [18] and modified by Napagoda et al, [19] was employed to determine the minimum inhibitory concentration (MIC) values of these formulations [19] where resazurin (0.1 mg/mL) was added to each microwell for the visual identification of the lowest concentration of test agent that prevents the growth of a bacterium. The content of the above microtitre plate wells was sub-cultured in agar plates to confirm the MIC values as well as to determine the minimum bactericidal concentration (MBC) of each formulation. The assay was conducted in triplicates.

The agar well diffusion assay was employed under anaerobic conditions for the determination of antibacterial activity against *P. acnes* following the method initially described by Valgas et al. [16] and modified by Nawarathne et al. [8]. The wells (diameter-6 mm, depth-5 mm) were prepared at equidistance in the blood agar (Oxoid) plates which were inoculated with clinical isolates of *P. acnes* obtained from the Medical Research Institute, Sri Lanka. The wells were filled with 50µL of each of the test formulations.

Thereafter, the agar plates were incubated at 37 ºC for 48 hours in an anaerobic jar and the zones of inhibition were measured in millimeter-scale after the incubation period. The experiments were conducted in triplicates.

2.6 Stability of the gel formulations

The gel formulations were stored at ambient temperature and the color, odor, homogeneity, washability, consistency, and pH were evaluated on day 30 after the preparation. The color, odor, homogeneity, and consistency were determined by physical/visual perception. The formulations were applied on the skin and then the ease extent of washing with water was checked to determine the washability. Further, the antibacterial activity of these gel formulations against *S. aureus* was also determined on day 30, to assess whether the antibacterial potential could be retained over a period of time during storage. Three replicates were used to determine the stability of each gel formulation.

3. RESULTS

3.1 Preliminary screening of the crude extracts for antibacterial activity

Among the three *C. sativum* extracts tested, the highest activity was observed in ethyl acetate extract with a zone of inhibition of 8.0± 0 mm in diameter while no measurable diameters were detected for both hexane and methanol extracts. Meanwhile, a zone of inhibition of 31± 0 mm was observed for the positive control, co-amoxiclav, however; the two negative controls, 2% DMSO and methanol did not exhibit any inhibition of the microbial growth. Therefore, further investigations were conducted using ethyl acetate extract which surpassed the other two extracts with respect to antibacterial potency.

This ethyl acetate extract was incorporated into the topical gel base at predetermined three different concentrations at which the growth of *S. aureus* and *P. acnes* could be inhibited. Figure 1 indicates that all the tested concentrations of ethyl acetate extract were capable of inhibiting the growth of S. *aureus* (diameter of the zone of inhibition was 7.5 ± 0, 8.0± 0, and 8.5 ± 0 mm for 5%, 10%, and 15% of the ethyl acetate extract respectively).

3.2 Antibacterial activity in the gel formulations

As indicated in Table 1, the highest activity was observed in formulation F3 which comprised 15% w/w of the seed extract and it effectively inhibited the growth of both

bacterial species. No zone of inhibition was detected for the negative controls, i.e. gel base and methanol, while the synthetic commercial anti-acne gel product (comprised of vitamin E, sulfur, isopropylmethylphenol, stearylglycyrrhetinate, vitamin B_6 as active ingredients) displayed zones of inhibition with a diameter of 8.3±1.5 and 10.5±0.7 mm against *S. aureus* and *P. acnes,* respectively.

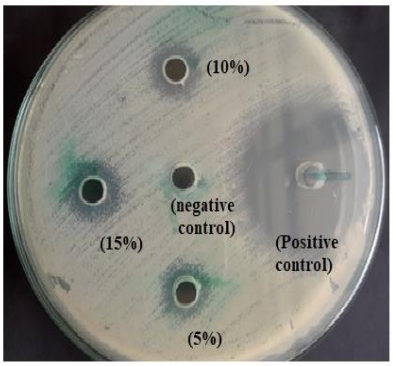

Figure 1: Results of the agar well diffusion test performed on three different concentrations (5%, 10%, and 15%) of the ethyl acetate extract against *S. aureus* to ensure that the incorporation above concentrations of ethyl acetate extract would offer an antibacterial effect to the resulting products

Table 1: *Antibacterial activity in three topical gel formulations against S. aureus and P. acnes*

Microorganism	**Diameter of the zone of inhibition (mm) resulting from each formulation**				
	F1	**F2**	**F3**	**Positive control**	**Negative control**
S. aureus	8.0±0.0	8.3±0.5	10.3±0.5	8.3±1.5	0.0±0.0
P. acnes	7.0±0.0	7.5±0.7	8.5±0.7	10.5±0.7	0.0±0.0

Note: F1: formulation comprised of 5% w/w extract, F2: formulation comprised of 10% w/w extract, F3: formulation comprised of 15% w/w extract

The MIC values against *S. aureus* were determined thereafter. MIC value of 250 µg/mL was observed for all the topical gel formulations while the MIC value of the synthetic commercial anti-acne gel was determined as 125 µg/mL, which is slightly more potent than that of the novel topical gel formulation F3.

3.3 Stability of gel formulations

All gel formulations demonstrated good stability, without any deterioration in the status of the initial physical parameters over a period of 30 days (Table 2). Apart from the aforementioned physical parameters, the antibacterial potency against *S. aureus* was also considered to assess the stability of the formulations. Here, zones of inhibition with a

diameter of 8.0± 0, 9.5±0.7, and 12±1.4 mm were observed for the formulations F1, F2, and F3 respectively even after 30 days, thus the antimicrobial properties of all three gel formulations against *S. aureus* have retained during the storage period.

Table 2: Comparison of the physical parameters of the topical gel formulations on Day 1 & Day 30

Formulation no:	No. of days after formulation	Color	Odor	Homogeneity	Water washability	Consistency	pH
F1	01	pale yellow	pleasant	Homogenous	washable	Semi-solid	6
	30	pale yellow	pleasant	Homogenous	washable	Semi-solid	6
F2	01	yellow	pleasant	Homogenous	washable	Semi-solid	5-6
	30	yellow	pleasant	Homogenous	washable	Semi-solid	5-6
F3	01	dark yellow	pleasant	Homogenous	washable	Semi-solid	5
	30	dark yellow	pleasant	Homogenous	washable	Semi-solid	5

4. DISCUSSION

The use of spices in cosmetic-pharmaceutical hybrid products is a novel trend employed by modern cosmeceutical manufacturers. These spices possess a very rich array of phytochemicals that are responsible for alleviating certain pathological conditions, for instance, polyphenolic compounds and terpenes like phytochemicals exert potent antibacterial, antioxidant, anti-tumor, anti-inflammatory, immune response modulatory, and analgesic like therapeutic effects. Thus, species like fennel, coriander, cumin, parsley, anise, and caraway which are rich in these phytochemicals have exhibited remarkable medicinal activity [20]. On this basis, the use of spices for the management of acne vulgaris is very favorable as spices are inherent with antibacterial, anti-inflammatory, and antioxidative effects.

Acne vulgaris is one of the most prevalent multifactorial dermatologic disorders characterized by the presence of colonization of *P.acnes* (currently called as *Cutibacterium*

acnes) and *Staphylococcus* species like *S. aureus* and *S. epidermidis.* Although it is not a life-threatening disease condition, the psychological burden on these patients may make them even more vulnerable to suicidal ideation in rare cases [21]. Acne can be classified as comedones (whiteheads and blackheads), papules, pustules, nodules, and cysts and a number of therapeutic agents are available to treat this condition. Although the prolonged use of antibiotics like erythromycin, clindamycin, nadifloxacin, and metronidazole is required to get rid of acne vulgaris flares, with the raising concerns of antibiotic resistance, those are usually prescribed as short courses. In addition, the antibiotics are frequently prescribed along with benzoyl peroxide, a non-antibiotic antimicrobial agent to reduce the incidence of resistance [22–24] despite the association of several adverse effects such as dryness, peeling and flaking with the use of benzoyl peroxide.

Hence, the application of natural remedies comprised of the spices like the seeds of *C. sativum* could be an alternative strategy to treat acne vulgaris. This was further supported by the recent research studies which reported the strong antibacterial activity of *C. sativum* against the acne-causing bacterial species *S. aureus* [25] as well as its antioxidant activity [26] since reactive oxygen species are attributable to the occurrence of acne [23]. Moreover, it has been documented that *C. sativum* could be used even as an antibiotic with other existing antibiotics such as chloramphenicol, gentamicin, cefoperazone, ciprofloxacin, tetracycline, piperacillin, and amphotericin to obtain a synergistic antibacterial and anti-fungal effect [25]. In addition, the possible utilization of C. *sativum* for dermatological issues was recorded by Vats and Sharma [14], where an anti-acne face gel was formulated from the seed oil of *C. sativum* [14].

However, our present study suggested that not only the seed oil, but also the seed extracts of *C. sativum* could also be effective in the management of acne flares while displaying a set of exceptional traits in our formulations that were absent in the gel formulations developed by Vats and Sharma [14]. The spices including the seeds of *C. sativum* can cause skin irritation which may lead to inflammation; especially in those who are hypersensitive to different irritants. Considering this fact, cetyl alcohol, an emollient and a moisturizer widely employed in the cosmetic industry was introduced into the gel base. Noteworthy, the consumers do not need to hesitate to use our novel products as those are devoid of parabens, a compound that has been subjected to controversies due to its carcinogenic

potential. Herein, parabens were substituted by phenoxy ethanol included as the preservative. Moreover, fuller's earth was employed as an additive into the base due to its capability of absorbing excessive sebum secreted by the sebaceous glands underneath the human skin. On the other hand, EDTA included in our novel gel base plays dual roles by stabilizing the formulations from rancidity and also assisting its water washability both of which could increase the consumer-friendly compliance of the product. In addition, rose water was used as the diluent and is supposed to assist in counterbalancing the pH of normal human skin while reducing the incidence of eczema, erythema, and dermatitis due to its inherent anti-inflammatory action. Interestingly, all the products developed in our study, lie in the range of pH 5-6 and it complies with the accepted optimal pH for human skin, 5.5.

Moreover, all the products displayed stability as reflected by the physical parameters and antibacterial potential. Hence, these findings are reflective of the significance of employing cosmeceuticals prepared with the seed extracts of *C. sativum* in the management of acne vulgaris. Therefore, future investigations, particularly with more clinical settings are warranted to ascertain the safety of these novel products on normal human skin and those clinical data will prove the efficacy and suitability of our novel formulations to develop and introduce as a commercial product into the market.

CONCLUSION

The topical gel formulations developed from seeds of *C. sativum* possessed prominent antibacterial potency against acne-causing bacteria *S. aureus* and *P.acnes*. The antibacterial activity was significant in the formulation comprising 15% w/w of the extract. The findings of this study suggest the possibility of employing seeds of *C. sativum* in the development of anti-acne formulations at a commercial scale and also rationalize the traditional utility of *C. sativum* as an anti-infectious and anti-inflammatory remedy.

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