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Review

Acne vulgaris: the skin microbiome, antibiotics and whether natural products could be considered a suitable alternative treatment?

Melissa Alston[1], Glyn Hobbs[1] and Ismini Nakouti[1]

1. Centre for Natural Products Discovery (CNPD), School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom.

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Author's Contact:

Email: I.Nakouti@ljmu.ac.uk

Tel.: +44-1512312077

Abstract

Acne vulgaris is a common, chronic inflammatory skin disease manifested as inflammatory and non-inflammatory lesions typically associated with *Cutibacterium acnes.* However, its pathogenesis is not fully understood nor is the complexity of the skin microbiome and how it contributes to the development of acne. Whilst acne is not a typical bacterial infection, antibiotics have been the mainstay of treatment for over 50 years.

Now, with the development of multi-drug resistant organisms and the emergence of resistant *C. acnes* strains; the question is are antibiotics still an appropriate treatment method or could natural products provide a suitable alternative? Research into alternative treatments is a growing field due to the increase in resistant organisms, there is a multitude of research into natural products due to their antimicrobial potential and the multiple mechanisms of action.

Melaleuca alternifolia is a key natural product of interest in the treatment of acne due to its documented use throughout history and its prevalence in over-the-counter treatments. Green Tea is a more recent natural product of interest due to its composition of polyphenols, which give rise to both antimicrobial and anti-inflammatory properties. However, research also suggests that a synergistic approach of natural products may be the way forward.

Keywords Acne vulgaris, skin microbiome, antibiotics, natural products.

INTRODUCCION

Acne vulgaris is a common, chronic inflammatory skin disease, ranking second as the most common dermatological condition (Xu and Li, 2019). It's prevalent in approximately 80% of all 11-30 years olds (Owen *et al*, 2017); despite its prevalence in young adults and adolescents it may persist into adulthood largely affecting females (Fox *et al*, 2016). This disease affects the pilosebaceous units of the skin resulting in the characteristic seborrhoea, non-inflammatory lesions (comedones) and inflammatory lesions (papules, pustules, nodules and cysts) as well as scarring, erythema and hyperpigmentation (Fox *et al*, 2016; Walsh, Efthimiou and Dréno, 2016). Dependent on the number and type of lesions, acne diagnosis is classified as mild, moderate or severe (Farrah and Tan, 2016). Lesions generally present in areas with a high proportion of sebaceous glands, such as, face, chest, upper back and upper arms (Fox *et al*, 2016; Owen *et al*, 2017; Walsh, Efthimiou and Dréno, 2016). Despite acne being a non-life-threatening skin condition (Greener, 2016), it has been associated with a negative psychological impact; although this may not always correlate with the clinical severity, it is often associated with self-perceived severity (Agnew, Leach and Segal, 2014). The psychological impact is considered substantial due to reports identifying an increased risk of acne patients developing insomnia, depression and anxiety (Trivedi *et al*, 2018); whilst also causing psychosocial symptoms such as embarrassment, emotional stress and maintaining relationships and friendships. Majority of the adverse psychological and psychosocial effects can be contributed to the discomfort, scarring and permanent disfigurement patients with severe acne suffer from (Fox *et al*, 2016). Therefore, effective treatment of acne is of great importance.

PATHOGENESIS OF *ACNE VULGARIS*

Pathogenesis of acne is a complex (Greener, 2016), multifactorial process that is still not fully understood (Dessinioti and Katsambas, 2017; Owen *et al*, 2017). It is thought to involve four major factors: a) enhanced sebum production, b) abnormal follicular hyperkeratinisation, c) an anaerobic, lipid-rich environment allowing *Cutibacterium acnes* to proliferate, d) host-inflammatory response and inflammation within the area (Farrah and Tan, 2016; Fox *et al*, 2016; Owen *et al*, 2017; Xu and Li, 2019; Walsh, Efthimiou and Dréno, 2016), as shown in Figure 1.

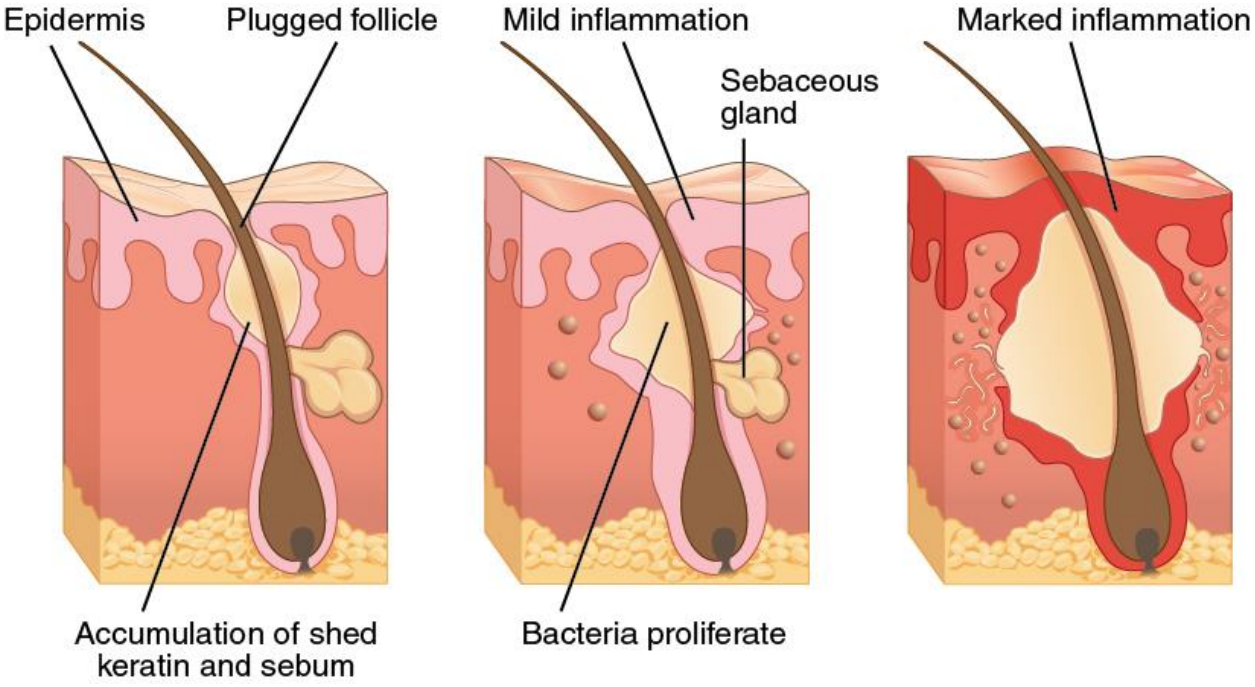

Figure 1 | A detailed image depicting the formation of acne (Betts *et al.*, 2013) (Creative Commons — Attribution 4.0 International — CC BY 4.0).

Although sebum has antibacterial functions, *C. acnes* hydrolyses triglycerides present in the secretions, releasing short chain free fatty acids such as propionic acid and porphyrins promoting bacterial colonisation of these glands (Grice and Segre, 2011; Dréno, 2017; Rocha and Bagatin, 2017; O'Neill and Gallo, 2018; Xu and Li, 2019). Porphyrins can generate reactive oxygen species, which have the ability to induce inflammation in keratinocytes resulting in the production of acne lesions via *C. acnes* binding to toll-like-receptor- 2(TLR-2) and TLR-4. *P. acnes* also has the capability to activate the classical and alternative complement pathways increasing the vascular permeability (Dréno, 2017; O'Neill and Gallo, 2018; Xu and Li, 2019; Platsidaki and Dessinioti, 2018).

Acne tends to present in adolescents as during puberty androgen hormones lead to an increased production of sebum which in turn promotes a high colonisation of *C. acnes* within the pilosebaceous follicle (Rocha and Bagatin, 2017; Platsidaki and Dessinioti, 2018). Thus, confirming that the microbial dysbiosis in acne could be attributed to the exacerbation of androgen-mediated seborrhoea and dysborhea (O'Neill and Gallo, 2018).

THE SKIN MICROBIOME

The skin microbiome is a complex ecological system (Christensen and Brüggemann, 2014; O'Neill and Gallo, 2018) that is unique to an individual (Christensen *et al*., 2016; Dréno, 2017); therefore, it is difficult to define a "healthy" skin microbiome (O'Neill and Gallo, 2018). The constituents of the microbial community include bacteria, viruses, fungi, protozoa and arthropods (Schommer and Gallo, 2013; Christensen and Brüggemann, 2014). Under normal physiological conditions, this ecosystem maintains homeostasis between the resident microbiome, transient microbes and the host when it is continuously being influenced by external and internal factors (Dréno *et al*., 2018; Schommer and Gallo, 2013; Dréno, 2017). Skin microbiome homeostasis is essential to healthy skin activity as it results in the inhibition of bacterial hyperproliferation of pathogenic commensals that are involved in various skin conditions (Xu and Li, 2019; Rocha and Bagatin, 2017).

When it comes to investigation of the skin microbiome, majority of research is regarding bacteria, this is possibly due to bacteria being the most prevalent microorganism to colonise the skin (Schommer and Gallo, 2013). There are four major phyla that dominate the skin: Actinobacteria, Proteobacteria, Bacteroidetes and Firmicutes (O'Neill and Gallo, 2018). Interestingly, these reflect the phyla that dominate the intestinal microbiome leading to the hypothesised skin-gut axis and why a high glycemic index diet is considered as a factor in the development of acne (Thursby and Juge, 2017; Salem, Ramser, Isham and Ghannoum, 2018). From these phyla more than 60% of the bacterial species belong to the genera *Staphylococcus*, *Corynebacterium* and *Propionibacterium* (Rocha and Bagatin, 2017. The most significant in the development of acne being that of *Cutibacterium acnes* and *Staphylococcus epidermidis* (Fox *et al*, 2016; Christensen *et al*., 2016).

Little is known regarding the skin virome possibly due to issues in the amplification of viruses in cell culture or limited antigenic and serological cross-reactivity; however, there is a controversial hypothesis that suggests pathogenic viruses such as the human papillomavirus (HPV) are part of the normal skin microbiome although this has not been fully elucidated (Schommer and Gallo, 2013).

Although, it is known that fungi are a constituent of a healthy skin microbiome, there is little information available regarding their ecological interaction in the state of health (Schommer and Gallo, 2013). However, it is known that *Malassezia spp.* have been detected in the follicles of patients with acne due to their favour of sebum lipids and was correlated with that of inflammatory acne (Christensen and Brüggemann, 2014). This could potentially indicate that *Malassezia* spp. could have a role in the development in acne although further investigations are needed alongside more research into the other constituents of the skin microbiome. Like the *Malassezia* spp., *Demodex folliculorum* favour lipid sebum and are found to inhabit the follicles (Schommer and Gallo, 2013).

Cutibacterium acnes

Cutibacterium acnes formally known as *Propionibacterium acnes* is an aerotolerant, anaerobic gram-negative bacilli which colonises the pilosebaceous follicles (Dréno *et al*., 2018; Esmael *et al*., 2019); therefore, it is more prevalent in areas which contain a large volume of these follicles such as the face, upper limbs and torso (Xu and Li, 2019). It has been proven that *P. acnes* is one of the most established

bacteria of the skin microbiome in both those with “healthy” skin and those with a form of acne (Dessinioti and Katsambas, 2017), although its presence is limited to the pilosebaceous follicles (Dréno *et al*., 2018; Fox *et al*, 2016).

A study by Fitz-Gibbon *et al* (2013), identified that certain *C. acnes* strains as shown in Table 1, were heightened in acne patients whilst others were predominantly found in individuals with a “healthy” skin microbiome. This is further clarified by Kwon, Yoon, Park and Suh, (2013) noted that although phylotype distribution was similar in skin surface and comedone lesion there was an increase in phylotype 1A-1 and a decrease in phylotype 1b and II in papules and pustules. Therefore, it was considered that phylotype 1A-1 was strongly associated with acne whilst phylotype II was associated with a “healthy” skin microbiome. In contrast to this an observational prospective study by Paugam *et al*, (2017) discovered no difference in the distribution of phylotypes between patients with mild and severe acne despite the phylotype 1A-1 being the most prevalent in both populations.

Despite being connected with the inflammatory condition acne, *C. acnes* also works to maintain the balance of the skin microbiome. It has the ability to limit the proliferation of pathogenic transient microbes, such as *Staphylococcus aureus* and *Streptococcus pyogenes*; via the hydrolysis of triglycerides in sebum releasing short-chain fatty acids aforementioned, which have antimicrobial properties in maintaining the acidic pH of the skin surface (Dréno, 2017; Xu and Li, 2019; O’Neill and Gallo, 2018). However, this then favours the growth of coagulase-negative *Staphylococci* and *Corynebacterial* growth (Grice and Segre, 2011).

Table 1 | A table identifying the different Clade formats against the ribotype and whether the strains are present in acne or healthy skin; with Clade 1 based on whole-genome sequence comparison whilst Clade 2 is based on Belfast *e*MLST and Clade 3 based on Aarhus MLST. (*e*MST expanded multi-locus sequence typing, MLST multi-locus sequence typing) (Xu and Li, 2019).

Clade 1	Clade 2	Clade 3	Ribotype	Acne	Healthy Skin
IA-1	IA1	I-1a	RT 1	Yes	Yes
IA-2	IA1	I-1a	RT4, RT5	Yes	No
IB-1	IA1	I-1b	RT8	Yes	No
IB-2	IA2	I-1a	RT3	Yes	Yes
IB-3	IB	I-2	RT1	Yes	Yes
IC	IC	NA	RT5	Yes	No
II	II	II	RT2, RT6	No	Yes
III	III	III	NA	No	No

Staphylococcus epidermidis

S. epidermidis is a coagulase-negative, facultative anaerobe coccus, which is a major skin commensal which occupies more than 27% of the total bacteria population (Christensen et al., 2016; Dréno et al., 2018). The successful colonisation of *S. epidermidis* is a result of its commensal lifestyle, which favours traits conferring persistency over aggressive host-damaging properties; with its low cytotoxicity and ability to evade host defences ensuring a low host immune response (Christensen and Brüggemann, 2014). Despite is prevalence it is not considered to be a causative agent of acne; in fact, it is suggested that there is an alliance between *S. epidermidis* and the host to keep potential transient pathogens from colonising the skin (Christensen and Brüggemann, 2014; Dréno, 2017; Rocha and Bagatin, 2018). Despite being a commensal of the skin, *S. epidermidis* has the ability to act as an opportunistic pathogen should it breach the skin surface and enter the bloodstream (Christensen and Brüggemann, 2014).

Antagonistic interactions between *S. epidermidis* and *C. acnes* are considered a common occurrence due to their close proximity to each other in the skin microbiome, although, the relevance in skin health and disease is greatly unknown (Christensen et al., 2016). However, a study by Christensen et al (2016) suggested that due to interspecies interaction there could a potential of disrupting the homeostasis of the

skin microbiome due to the various inhibition mechanisms that *S. epidermidis* possesses in relation to C. acnes. Although this study could not confirm the relevance of these interactions in skin disorders.

Antibiotic Treatment

Antibiotics have been the mainstay of acne treatment for over 50 years even though acne is not a bacterial infection but could be considered an inflammatory reaction to the skin microbiome (Humphrey, 2012; Greener, 2016; Walsh, Efthimiou and Dréno, 2016). Antibiotic treatment in acne involves the use of oral and or topical antibiotics intended to reduce the quantity of *P. acnes* colonising the pilosebaceous follicle, as it is understood that *P. acnes* is the principal bacteria involved in the pathogenesis of acne lesions (Farrah and Tan, 2016; Humphrey, 2012). However, some antibiotics specifically cyclines have significant anti-inflammatory properties which inhibit the production of *C. acnes* associated inflammatory mediators; suggesting that antibiotics have a more important role than the antimicrobial activity (Walsh, Efthimiou and Dréno, 2016; Humphrey, 2012; Greener, 2016). Although, this has not yet been reported in vivo, the suggestion is hypothesised based on the copious in vitro data which identifies that antibiotics have activities unrelated to eradicating bacteria (Walsh, Efthimiou and Dréno, 2016).

Whilst reducing the quantity of *P. acnes* may seem to improve acne, it may not resolve or cure the condition (Farrah and Tan, 2016). In fact, antibiotics can cause dysbiosis of the microbiome, potentially encouraging the emergence of pathogenic transient bacteria such as S. aureus, Methicillin-Resistant S. aureus (MRSA) and other resistant bacteria (Greener, 2016). This can potentially lead to the host developing infections from pathogenic and highly resistant organisms should they breach the skin barrier and defence mechanisms. With topical antibiotics this is limited to the area treated; however with oral antibiotics the body as a whole may be affected (Walsh, Efthimiou and Dréno, 2016).

ANTIMICROBIAL RESISTANCE IN ACNE

According to the O'Neill Report (2016), antimicrobial resistance is a major threat to public health worldwide and is still on the rise, impacted by the overuse of antimicrobials, which in turn has increased the rate in which resistance is developing. It is estimated that by 2050, 10 million lives per year are at risk due to the development of drug-resistant infections. It currently stands at 700,000 deaths per year, which is an increase of 1430%. The use of antibiotics in acne is vastly contributing to this risk with the prevalence of resistant strains of *P. acnes* being observed over the years (Humphrey, 2012).

There was no evidence of antibiotic resistant *C. acnes* in the skin microbiome of over 1000 patients in 1976 (Leyden, 1976), yet, by 1979 Crawford and colleagues discovered the first indications of resistance, specifically to topical erythromycin and clindamycin followed by tetracycline. Since this development, antibiotic resistance in acne has continued to rise globally with incidence reaching of 20% in 1978 reaching 62% in 1996 (Walsh, Efthimiou and Dréno, 2016). It is thought that resistant strains of *C. acnes* can emerge relatively quickly as a result of chromosomal point mutations mainly in the 23S rRNA gene for macrolide resistance and 16S rRNA for tetracycline resistance (Dréno et al., 2018; Greener, 2016; Humphrey, 2012). However, *C. acnes* is naturally a relatively resilient organism with variants having the ability to withstand antibiotic treatment without resistance (Walsh, Efthimiou and Dréno, 2016); therefore, this could favour some of the conflicting evidence that resistant strains remain after treatment (Farrah and Tan, 2016).

Evidence suggests that *C. acnes* colonies in the pilosebaceous follicle develop macrocolonies resulting in the production of large biofilms, which are notoriously difficult to eradicate due to their intrinsic properties of increased tolerance to antibiotics (Hall and Mah, 2017; Dréno et al., 2018). It is suggested that planktonic and sessile cells do not share identical transcriptomes or proteomes, therefore, indicating that there were phenotypic differences between the two (Resch, Rosenstein, Nerz and Gotz, 2005; Hall and Mah, 2017). This could be confirmed by the work of Jahns et al (2012), who found no qualitative differences between *C. acnes* biofilms in acne and controls; instead, it was inferred that it was phenotypic changes rather than genetic changes that accounted for the pathogenic role of *C. acnes* in acne. This confers the data that identifies aforementioned phylotype 1A-1 as being highly associated with erythromycin and clindamycin resistant *P. acnes* strains (Dréno et al., 2018).

ANTIBIOTIC GUIDELINES IN ACNE

Despite acne not being a typical bacterial infection, antibiotics are still considered to have a role in the treatment of moderate to severe acne. However, there has been guidelines put in place to ensure that effective usage of this important medication as shown in Table 2.

Table 2 | A table to identify the numerous guidelines by the Global Alliance to Improve Outcomes in Acne, The European-Evidence-based Guidelines for the Treatment of Acne and the American Academy of Dermatology that have been put into place in order to limit the further development of antibiotic resistance in acne (Humphrey, 2012; Farrah and Tan, 2016; Walsh, Efthimiou and Dréno, 2016).

	Guidelines around Antibiotic Treatment in Acne
1	Avoid Topical or Oral Antibiotics as monotherapy
2	Avoid topical or Oral Antibiotics as Maintenance Therapy
3	Limit the duration of antibiotic use (3 months or less)
4	The use of oral antibiotics only in moderate & moderately severe acne
5	Oral Antibiotics only used as Induction Therapy
6	Use of Oral Erythromycin & other macrolides restricted to cases where cyclines are contraindicated or not tolerated
7	Oral Clindamycin is not recommended for acne treatment
8	Mild to Moderate acne treatment should be combined with a non-antimicrobial topical agent
9	Topical agents such as retinoids or Benzoyl peroxide added to the treatment regime

These current guidelines in place come from various institutions, such as Global Alliance to Improve Outcomes in Acne, The European-Evidence-based Guidelines for the Treatment of Acne and the American Academy of Dermatology in order to minimise the effect of antibiotic resistance in acne. It is thought that these guidelines could limit the transfer of resistant genes to potentially pathogenic bacteria, which could present difficult clinical challenges especially if the resistant genes were relative to the first line systemic agents for the treatment of MRSA (minocycline, trimethoprim-sulfamethoxazole, clindamycin and doxycycline) [Humphrey, 2012; Farrah and Tan, 2016; Walsh, Efthimiou and Dréno, 2016].

However, even though these guidelines have been put in place researchers have found that treatment does not always follow the recommendations and guidelines in place (Greener, 2016). The analysis of 928 acne patients by Whitehouse et al in 2016, discovered that on average the patients received oral antibiotics for 6.5 months compared to the recommended time of 3 months or less: thus, resulting in the lengthy exposure of antibiotics allowing the virulent strains of *P. acnes* to potentiate resistance and potentially confer to other bacteria colonising the skin microbiome.

There are some countries which have limited the use of antibiotics to treat acne which has resulted in low resistance levels being identified; emphasising the need for the global economy to reduce their use in relation to this chronic condition (Ross et al, 2003; Sardana and Garg, 2014). With the levels of resistance correlating to the levels of antibiotics use (Walsh, Efthimiou and Dréno, 2016; Humphrey, 2012) and the risk of further antibiotic resistance in mind, the consequence of causing dysbiosis in the microbiome of an individual attempting to treat a non-infectious *P. acnes* biofilm; the question becomes whether antibiotics are really a suitable treatment or are there alternative treatment methods available?

COMPLEMENTARY AND ALTERNATIVE THERAPIES

The term complementary and alternative medicine (CAM) therapies covers a vast array of products and procedures that can be of use in the treatment of acne; however, the specific area of interest here is botanicals. The use of plant extracts and herbs as a means of treatment originated in ancient Egypt and Greece from as early as 4500BC to between 500 and 400BC retrospectively (Elshafie and Camele, 2017). Due to the development of multi-drug resistant organisms, the interest in botanicals as alternative treatment methods has greatly increased possibly due to their added benefit of possessing several modes of action due to their chemical composition (Fox et al, 2016).

One of the main categories of botanicals researched is essential oils (EO). EO are volatile secondary metabolites produced by various plant components, with around 300 EO available commercially (Wińska et al., 2019). They are comprised of complex organic chemical arrangements which includes compounds

such as alcohols, aldehydes, terpenes and phenols, which are known to give rise to their various antimicrobial properties with some plants even possessing anti-inflammatory properties (Fox et al, 2016; Tariq et al, 2019). Due to the perception as being “natural” rather than allopathic medicines they are believed to be safe and non-toxic due to their longstanding usage over many centuries; however, this is a misconception, there are many scientific studies which have highlighted that EO have the ability to produce adverse effects with the most common being that of skin irritation or allergic contact dermatitis due to their topical use (Orchard and van Vuuren, 2017; Winkelman, 2018).

Tea Tree oil

M. alternifolia (Maiden & Betche) Cheel of the family Myrtaceae -commonly known as Tea Tree oil (TTO)- is one of the most well-recognised EO due to its medicinal use over a number of decades; it is the product of the Melaleuca alternifolia shrub endemic to Australia and was traditionally used by aboriginals in the treatment of cold and wounds (Plant, Dinh, Argo and Shah, 2019).

Due to the quantity of patients that self-treat acne with TTO and its presence in several over the counter acne products an international standard has been formulated for its use (Winkelman, 2018; Fox et al, 2016).

There has been ample research regarding the effect of TTO on acne due to its constituents. As TTO is composed of terpene hydrocarbons, monoterpenes, sesquiterpenes and associated alcohols, with the major component being that of terpinen-4-ol (Figure 2), which should comprise more than 30% of the TTO concentration and 1,8-cineole less than 15% concentration according to the International Organisation for Standardisaton (Lee et al, 2013). This is due to 1,8-cineole being considered as the undesirable allergen in TTO, potentially responsible for the skin irritation as adverse reactions to TTO tend to fade as its concentration diminishes which unintentionally inverts the proportion in favour of Terpinen- 4-ol (Pazyar, Yaghoobi, Bagherani and Kazerouni, 2012). A study by Lee et al, (2013) identified that whilst Terpinen-4-ol exhibits strong antimicrobial and anti-inflammatory properties, the minor components do contribute to the overall antimicrobial effects of TTO.

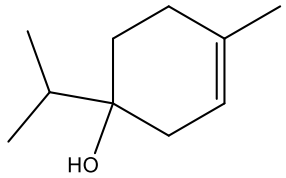

Figure 2 | Terpinen-4-ol

Whilst Lee et al (2013) investigated the antimicrobial effects of the components of TTO, clinical research into the effect of TTO on acne has been performed by numerous researchers. Bassett, Barnetson and Pannowitz, (1990) compared 5% TTO gel with 5% Benzoyl peroxide (BPO) in the treatment of mild to moderate acne in a single-blind trial. It was found that both TTO and BPO has a significant effect in reducing the number of inflammatory and non-inflammatory lesions. However, the onset of action was slower in TTO but fewer side effects were experienced. Further research by Enshaieh, Jooya, Siadat and Iraji (2007) compared 5% TTO to a placebo in a double-blind placebo-controlled study. TTO was found to reduce both inflammatory and non-inflammatory lesions in patients with mild to moderate acne. TTO was proven to be 3.55 times and 5.75 times more effective in reducing total lesion counts (TLC) and acne severity index scores (ASI) in comparison to the placebo. This study further clarified the work by Bassett, Barneston and Pannowitz (1990) in confirming the effectiveness of TTO as an acne treatment.

Most EO are used in blends or synergisms with the intention to create an effect where the combination is more powerful than the individual product (Orchard and van Vuuren, 2017); this information alongside earlier research provided a basis for investigations of TTO alongside other natural products. Mazzarello et al, (2018) produced two double-blind investigations surrounding the effect of a product containing 20% propolis, 3% TTO and 10% Aloe vera (PTAC) as they had proven antibacterial and anti-inflammatory properties. This was compared to 3% erythromycin cream. Results indicated that although PTAC did not possess sebum-reducing properties it did improve the erythema index of papules and erythematous scarring greater than the erythromycin cream. In fact, PTAC reduced the ASI score by 68% and TLS by 64% after 30 days usage in comparison to the 50% and 47% retrospectively for erythromycin cream. This study proves that natural products can be considered as an alternative treatment method to antibiotics.

The abundance of research on the use of TTO seems to indicate that it would be suitable and beneficial as an acne treatment; with TTO synergism with other natural products as an additional area of investigation. However, more clinically controlled trials need to be completed for it to be taken seriously as a medical alternative to antibiotics. In the meantime, perhaps the popularity of TTO over the counter products can bridge this gap.

Green Tea extracts

Despite it not being an EO, Camellia sinensis (L.) Kuntze (Theaceae) -commonly known as Green Tea (GT)- is another natural product that has gained interest in recent years due to its composition of polyphenols which are found in abundance in a variety of foods such as nuts, wine, vegetables and various teas which gives rise to anti-inflammatory and antimicrobial properties (Fox et al, 2016). Tea is the second most consumed beverage worldwide and therefore an important source of plant polyphenols so it is understandable that the antimicrobial properties of GT would be of interest in acne treatment (Saric, Notay and Sivamani, 2016). GT polyphenols are primarily composed of catechins of which there are several that make up the 30-42% of the extracted solid weight percentage; with the remainder being composed of flavonols (Saric, Notay and Sivamani, 2016). The most abundant catechin in GT is that of epigallocatechin-3-gallate (EGCG) (Figure 3)

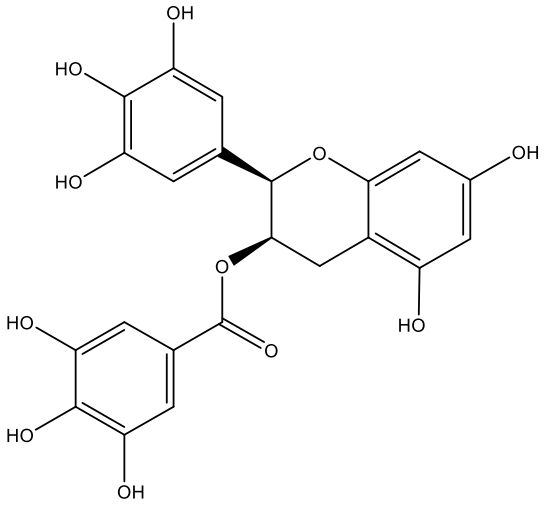

Figure 3 | (−)-Epigallocatechin gallate

Investigation into EGCG and GT has progressed over the years moving from in vitro to clinical studies with a recent study involving the ingestion of GT capsules to investigate its effects on acne (Yoon et al, 2013, Mahmood, 2013; Lu and Hsu, 2016). One of the major contributors into the effect of this natural product is by Yoon et al, (2013) who initially performed an in vitro study analysing the effects of EGCG and identified that this compound has the ability to act on three of the pathological processes of acne pathogenesis; it can suppress sebum production, inhibit the growth of *C. acnes* whilst promoting anti-inflammatory effects. Therefore, Yoon et al, moved to a double-blind split body face trial to investigate the effects of a 1% and 5% EGCG topical in comparison to a 3% ethanol topical. Each group (1% or 5% EGCG) applied the topical to one side of their face and the ethanol vehicle to the other. After eight weeks, the patients were assessed and non-inflammatory lesions were reduced alongside inflammatory lesions by 79% and 89% retrospectively for the 1% ECGC group; the 5% group showed parallel improvement.

The work by Yoon et al, (2013) was further clarified in a study by Mahmood et al, (2013) who investigated the effects of a 5% GT topical and 2.5% GT in combination with a 2.5% lotus extract (GTL) topical on facial sebum production. Results from this study shows that the group receiving the GT topical displayed a 27% reduction in sebum production from baseline where those that applied the GTL topical showed a 25% reduction. Although those receiving the GTL showed a smaller percentage reduction, the sebum secretion reduction was to a higher degree. However, a study by Lu and Hsu, (2016) investigated whether green tea supplementation could improve acne. They used 1500mg decaffeinated green tea daily (three 500mg capsules after meals) in comparison to a cellulose control; after four weeks there was no significant difference in lesion counts. This study identifies the need for topical therapies in acne.

Despite the lack of results from Lu and Hsu (2016) regarding GT supplements, there is still ample research to favour the use of GT as an acne treatment, especially given the results of GT and lotus synergism. Further research into GT synergism could be a productive move forward.

CONCLUSION

The treatment of acne is an important area of research and is gaining momentum to further understand the pathogenesis of the condition and any new potential target areas. Whilst it is known that *C. acnes* is a major contributor to the development of acne lesions, targeting of the inflammatory pathways that are initiated as a result of *C. acnes* seems a natural response. Whilst it is apparent that acne is not a typical bacterial infection but treatment with antibiotics alleviates the symptoms somewhat; consideration needs to be made as to whether this is the correct course of action with multi-drug resistant organisms on the rise and the ability of *C. acnes* strains to produce resistance relatively quickly. With CAM therapies now an area of interest specifically EO due to their complexity how that translates into multiple mechanisms of action, there is a suggestion that resistance to these natural products is less likely to develop, with no significant antimicrobial resistance reported thus far. With the copious research regarding the antimicrobial and anti-inflammatory properties of EO evident it seems obvious that they would make a suitable alternative to antibiotics. Withholding the use of antibiotics in acne has already been seen to translate into lower resistance levels in some countries; accepting the same response in every country could result in the levels of resistance being maintained if not lowered globally.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Agnew, T., M.L., Segal, L. 2014. The Clinical Impact and Cost-Effectiveness of Essential Oils and Aromatherapy for the Treatment of Acne Vulgaris: A Protocol for a Randomized Controlled Trial. The Journal of Alternative and Complementary Medicine, 20, 399-405.

Bassett, I., Barnetson, R. and Pannowitz, D., 1990. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Medical Journal of Australia, 153(8),455-458.

Betts J.G., Young K.A., Wise J.A., Johnson E., Poe B., Kruse D.H., Korol O., Johnson J.E., Womble M., DeSaix P.. 2013Anatomy and Physiology. OpenStax. Houston, Texas.Book URL: https://openstax.org/books/anatomy-and-physiology/pages/1-introduction Section URL: https://openstax.org/books/anatomy-and-physiology/pages/5-4-diseases-disorders-and-injuries-of-the-integumentary-system

Christensen, G. and Brüggemann, H. (2014). Bacterial skin commensals and their role as host guardians. Beneficial Microbes, 5(2), 201-215.

Brzuszkiewicz, E., Lomholt, H. and Brüggemann, H. 2016. Antagonism between Staphylococcus epidermidis and Propionibacterium acnes and its genomic basis. BMC Genomics, 17(152), pp.1-14.

Crawford, W., Crawford, I., Stoughton, R. and Cornell, R., 1979. Laboratory Induction and Clinical Occurrences of Combined Clindamycin and Erythromycin Resistance in Corynebacterium acnes. Journal of Investigative Dermatology, 72(4),187-190.

Department of Health., 2016. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Presented to the UK Prime Minister [online] London: Department of Health. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [Accessed 21st October 2019]

Dessinioti, C., Katsambas, A., 2017. Propionibacterium acnes and antimicrobial resistance in acne. Clinics in Dermatology, 35, 163-167.

Dréno, B. (2017). What is new in the pathophysiology of acne, an overview. Journal of the European Academy of Dermatology and Venereology, 31(5),8-12.

Dréno, B., Pécastaings, S., Corvec, S., Veraldi, S., Khammari, A. and Roques, C., 2018. Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates. Journal of the European Academy of Dermatology and Venereology, 32(2),5-14.

Elshafie, H. and Camele, I., 2017. An Overview of the Biological Effects of Some Mediterranean Essential Oils on Human Health. BioMed Research International, 2,1-14.

Enshaieh, S., Jooya, A., Siadat, A. and Iraji, F., 2007. The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: A randomized, double-blind placebo-controlled study. Indian Journal of Dermatology, Venereology and Leprology, 73(1),22.
Esmael, A., Hassan, M., Amer, M., Abdelrahman, S., Hamed, A., Abd-raboh, H. and Foda, M., 2019. Antimicrobial activity of certain natural-based plant oils against the antibiotic-resistant acne bacteria. Saudi Journal of Biological Sciences, 27(1),448-455.
Farrah, G., Tan, E., 2016. The use of oral antibiotics in treating acne vulgaris: a new approach. Dermatologic Therapy, 29, 377-384.
Fitz-Gibbon, S., Tomida, S., Chiu, B., Nguyen, L., Du, C., Liu, M., Elashoff, D., Erfe, M., Loncaric, A., Kim, J., Modlin, R., Miller, J., Sodergren, E., Craft, N., Weinstock, G. and Li, H., 2013. Propionibacterium acnes Strain Populations in the Human Skin Microbiome Associated with Acne. Journal of Investigative Dermatology, 133(9),2152-2160.
Fox, L., Csongradi, C., Aucamp, M., du Plessis, J. and Gerber, M., 2016. Treatment Modalities for Acne. Molecules, 21(1063),1-20.
Greener, M., 2016. Managing acne: The importance of considering resistance. British Journal of School Nursing, 11(7),332-335.
Grice, E. and Segre, J., 2011. The skin microbiome. Nature Reviews Microbiology, 9(4), pp.244-253.
Hall, C. and Mah, T., 2017. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMS Microbiology Reviews, 41(3),276-301.
Humphrey, S., 2012. Antibiotic Resistance in Acne Treatment. Skin Therapy Letter, 17(9),1-7.
Jahns, A., Lundskog, B., Ganceviciene, R., Palmer, R., Golovleva, I., Zouboulis, C., McDowell, A., Patrick, S. and Alexeyev, O., 2012. An increased incidence of Propionibacterium acnes biofilms in acne vulgaris: a case-control study. British Journal of Dermatology, 167(1),50-58.
Kwon, H., Yoon, J., Park, S. and Suh, D., 2013. Analysis of distribution patterns of Propionibacterium acnes phylotypes and Peptostreptococcus species from acne lesions. British Journal of Dermatology, 169(5),1152-1155.
Lee, C., Chen, L., Chen, L., Chang, T., Huang, C., Huang, M. and Wang, C., 2013. Correlations of the components of tea tree oil with its antibacterial effects and skin irritation. Journal of Food and Drug Analysis, 21,169-176.
Leyden, J.J.,1976. Antibiotic resistance acne. Cutis, 17, 593-596.
Lu, P. and Hsu, C., 2016. Does supplementation with green tea extract improve acne in post-adolescent women? A randomized, double-blind, and placebo-controlled clinical trial. Complementary Therapies in Medicine, 25,159-163.
Mahmood, T., Akhtar, N. and Moldovan, C., 2013. A comparison of the effects of topical green tea and lotus on facial sebum control in healthy humans. Hippokratia, 17(1),64-67.
Mazzarello, V., Donadu, M., Ferrari, M., Piga, G., Usai, D., Zanetti, S. and Sotgiu, M., 2018. Treatment of acne with a combination of propolis, tea tree oil, and Aloe vera compared to erythromycin cream: two double-blind investigations. Clinical Pharmacology: Advances and Applications, 10,175-181.
O'Neill, A. and Gallo, R., 2018. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris. Microbiome, 6(177),1-16.
Orchard, A. and van Vuuren, S., 2017. Commercial Essential Oils as Potential Antimicrobials to Treat Skin Diseases. Evidence-Based Complementary and Alternative Medicine, 2017,1-92.
Owen, O., M.G., Aroo, R., Ruiz-Rodado, V., Price, P., Laird, K. 2017. A Multifactorial Comparison of Ternary Combinations of Essential Oils in Topical Preperations to Current Antibiotic Prescription Therapies for the Control of Acne Vulgaris-Associated Bacteria. Phytotherapy Research, 31, 410-417.
Paugam, C., Corvec, S., Saint-Jean, M., Le Moigne, M., Khammari, A., Boisrobert, A., Nguyen, J., Gaultier, A. and Dréno, B., 2017. Propionibacterium acnes phylotypes and acne severity: an observational prospective study. Journal of the European Academy of Dermatology and Venereology, 31(9), 398-399.
Pazyar, N., Yaghoobi, R., Bagherani, N. and Kazerouni, A., 2012. A review of applications of tea tree oil in dermatology. International Journal of Dermatology, 52(7),784-790.
Plant, R., Dinh, L., Argo, S. and Shah, M., 2019. The Essentials of Essential Oils. Advances in Pediatrics, 66(2019), 111-122.
Platsidaki, E. and Dessinioti, C. (2018). Recent advances in understanding Propionibacterium acnes (Cutibacterium acnes) in acne. F1000Research, 7, 1953.

Resch, A., Rosenstein, R., Nerz, C. and Gotz, F., 2005. Differential Gene Expression Profiling of Staphylococcus aureus Cultivated under Biofilm and Planktonic Conditions. Applied and Environmental Microbiology, 71(5), 2663-2676.
Rocha, M. and Bagatin, E., 2017. Skin barrier and microbiome in acne. Archives of Dermatological Research, 310,181-185.
Ross, J., Snelling, A., Carnegie, E., Coates, P., Cunliffe, W., Bettoli, V., Tosti, G., Katsambas, A., Galvan Perez Del Pulgar, J., Rollman, O., TOrOk, L., Eady, E. and Cove, J., 2003. Antibiotic-resistant acne: lessons from Europe. British Journal of Dermatology, 148(3),467-478.
Salem, I., Ramser, A., Isham, N. and Ghannoum, M., 2018. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Frontiers in Microbiology, 9,1-14.
Sardana, K. and Garg, V., 2014. Antibiotic resistance in acne: is it time to look beyond antibiotics and Propionobacterium acnes? International Journal of Dermatology, 53(7), 917-919.
Saric, S., Notay, M. and Sivamani, R., 2016. Green Tea and Other Tea Polyphenols: Effects on Sebum Production and Acne Vulgaris. Antioxidants, 6,2.
Schommer, N. and Gallo, R., 2013. Structure and function of the human skin microbiome. Trends in Microbiology, 21(12),660-668.
Tariq, S., Wani, S., Rasool, W., Shafi, K., Bhat, M., Prabhakar, A., Shalla, A. and Rather, M., 2019. A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens. Microbial Pathogenesis, 134(2019),103580.
Thursby, E. and Juge, N., 2017. Introduction to the human gut microbiota. Biochemical Journal, 474(11), pp.1823-1836. Treatment Modalities for Acne. Molecules, 21, 1-20.
Walsh, T.R., Efthimiou, J., Dreno, B. 2016. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. The Lancet, 16, 22-32.
Whitehouse, H., Fryatt, E., El-Mansori, I., Layton, A.M., 2016. Oral antibiotics for acne: are we adopting premium use? British Journal of Dermatology, 175, 91
Winkelman, W., 2018. Aromatherapy, botanicals, and essential oils in acne. Clinics in Dermatology, 36,299-305.
Wińska, K., Mączka, W., Łyczko, J., Grabarczyk, M., Czubaszek, A. and Szumny, A., 2019. Essential Oils as Antimicrobial Agents—Myth or Real Alternative? Molecules, 24, 2130.
Xu, H., Li, H. 2019. Acne, the Skin, and Antibiotic Treatment American Journal of Clinical Dermatology, 20, 335-344.
Yoon, J., Kwon, H., Min, S., Thiboutot, D. and Suh, D., 2013. Epigallocatechin-3-Gallate Improves Acne in Humans by Modulating Intracellular Molecular Targets and Inhibiting P. acnes. Journal of Investigative Dermatology, 133(2),429-440.