ROS

REVIEW ARTICLE

Natural Polyphenols for Acne Vulgaris: Clinical Evidence and Biological Mechanisms

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ABSTRACT | Acne vulgaris (acne for short) inflicts virtually all teenagers and young adults and is the number one most common skin disease globally. It is an inflammatory disease causing tremendous esthetical and phycological burden. Although conventional medical therapy can be effective in treating acne, drugs, especially those requiring a prescription, can cause many adverse effects. This leads to the increasing use of natural compound-based modalities, including polyphenols, in the management of acne. Polyphenols, present in large quantities in fruits, vegetables, and green tea, exert diverse biological effects, including anti-inflammatory and antibacterial activities. Among the natural polyphenols, resveratrol from grapes, and epigallocatechin-3-gallate (EGCG) from green tea, have recently been shown to be effective in treating inflammatory acnes. Cosmeceutical products containing resveratrol or EGCG are emerging natural remedies for treating acne patients without causing noticeable adverse effects. This mini-review summarizes recent research findings on the clinical efficacy and biological mechanisms of resveratrol and EGCG in treating inflammatory acne.

KEYWORDS | Acne vulgaris; Anti-inflammation; Epigallocatechin-3-gallate; Green tea; Polyphenols; Resveratrol

ABBREVIATIONS | EGCG, epigallocatechin-3-gallate; IGF-1, insulin-like growth factor 1

CONTENTS

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1. INTRODUCTION

Acne vulgaris (acne for short) inflicts virtually all adolescents and young adults and ranks the number one most common skin disease in the world. It is the most familiar, yet notorious, malady causing a tremendous esthetical and psychological burden. Although the disease can be controlled by treatment with various conventional drugs, the remarkable adverse effects associated with these drugs have been increasingly pushing many persons with acne to seek more tolerable alternative therapies, particularly the natural compound-based modalities.

Plant-derived polyphenols possess diverse biological properties, including cardiovascular protection and anticancer activity [1]. The past decade has also witnessed the clinical studies on these compounds, especially the grape-derived resveratrol and the green tea-derived epigallocatechin-3-gallate (EGCG), in the treatment of acne. In this mini-review, I first provide an overview on natural polyphenols and then discuss the recent clinical research showing an anti-acne efficacy for resveratrol- and EGCG-based cosmeceuticals as well as the underlying biological mechanisms.

2. OVERVIEW OF NATURAL POLYPHENOLS

Phenolic compounds, frequently called phenols or phenolics, are a class of chemicals consisting of one or more hydroxyl group (–OH) bonded directly to one or more six-membered aromatic rings. The simplest member of the class is phenol (C_6H_5OH), which is a monophenol. Polyphenols are those that contain more than one hydroxyl group.

2.1. Natural Occurrence

Polyphenols are widely distributed in plants. Fruits and vegetables as well as wine and tea constitute the major dietary sources of polyphenols, with an average consumption of approximately one gram per day for a normal human adult [2, 3].

2.2. Classification of Dietary Polyphenols

Dietary polyphenols are generally classified into five major groups, as listed below. As shown, resveratrol is a member of the second group—stilbenes.

(1) Flavonoids (e.g., epigallocatechin-3-gallate)
(2) Stilbenes (e.g., resveratrol)
(3) Phenolic acids (e.g., caffeic acid)
(4) Lignans (e.g., secoisolariciresinol)
(5) Others (e.g., curcumin)

2.3. Classification of Natural Flavonoids

Flavonoids, the most commonly studied dietary polyphenols, share a common structure consisting of two aromatic rings that are bound together by three carbon atoms that usually form an oxygenated heterocycle (**Figure 1**). Flavonoids represent a large family of natural polyphenols and are further classified into the following six subclasses, with EGCG being a member of the flavanol subclass.

(1) Flavonols (e.g., quercetin)
(2) Flavones (e.g., luteolin)
(3) Isoflavones (e.g., genistein)
(4) Flavanones (e.g., taxifolin)
(5) Anthocyanidins (e.g., delphinidin)
(6) Flavanols (e.g., epigallocatechin-3-gallate)

3. RESVERATROL

3.1. Natural Sources and Biological Activities

As noted above, resveratrol is a stilbene polyphenol. It is perhaps the most famous natural phenolic compound studied in biology and medicine. Resveratrol is actually a phytoalexin (a compound that suppress-

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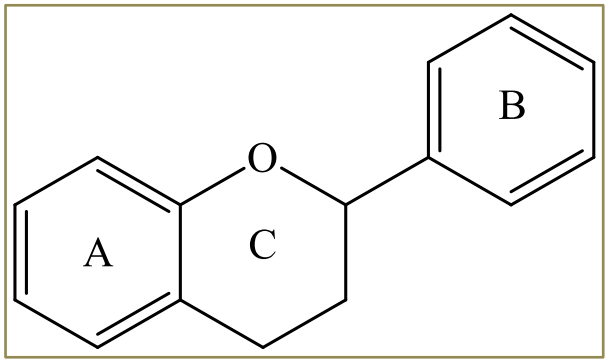

FIGURE 1. The basic chemical structure of natural flavonoids. As depicted, the shared core structure of flavonoids consists of 3 aromatic rings.

es plant pathogens) produced by diverse plants in response to injury or attack by plant pathogens (e.g., bacteria, fungi, insects). Resveratrol is found in fruits (e.g., red grapes, blueberries, raspberries, mulberries), nuts (e.g., peanuts, pistachios), and cocoa beans. It is present in red wine at various concentrations depending on the wine brand. Notably, peanuts are a significant source of dietary resveratrol, and one gram of peanuts may provide up to 1.8 µg resveratrol [4].

Studies over the past decades have demonstrated a number of beneficial effects of resveratrol in biological systems, including its antioxidant and anti-inflammatory activities and the potential to protect against many diseases and conditions, such as cardiovascular disorders, metabolic syndrome and diabetes, cancer, neurodegeneration, and aging in animal models [5]. Randomized controlled trials over the past few years have shown a potential efficacy for pharmacological doses of resveratrol in the intervention of such human diseases as obesity [6] and diabetes [7]. In addition, as described below, clinical studies have also revealed an anti-acne efficacy of resveratrol.

3.2. Cosmeceutical Products

The popularity of resveratrol in health promotion is reflected by the availability of diverse dietary supplements and cosmeceutical products that contain resveratrol. **Figure 2** shows the chemical structure of resveratrol and the picture of a resveratrol-based cosmeceutical cream for acne-prone skin.

3.3. Clinical Evidence

The clinical anti-acne efficacy of a resveratrol-containing hydrogel (1 µg/g) was investigated in a single-blind, vehicle-controlled, split-face study on 20 Italian patients with mild-to-moderate inflammatory acne [8]. The resveratrol-containing hydrogel was applied daily as a solo treatment on the right side of the face for 60 days, while the hydrogel vehicle was applied on the left side of the face as a control. All patients were satisfied with the active treatment and none experienced adverse effects. Clinical evaluation showed a 54% reduction in acne severity as assessed by the Global Acne Grading system on the resveratrol-treated sides of the face compared with a 6% reduction on the vehicle-treated sides of the face. Histologic analysis showed a 67% reduction in the average area of microcomedones on the resveratrol-treated sides of the face compared with a 10% reduction on the vehicle-treated sides of the face [8]. The study concluded that the resveratrol-containing hydrogel is highly effective for reducing both microcomedones and inflammatory lesions; however, its efficacy needs to be further established via large randomized controlled trials.

3.4. Biological Mechanisms

The efficacy of topical resveratrol in treating acne may result from its well established anti-inflammatory and antioxidant activity [9], as well as its inhibition of *P. acnes* bacterial proliferation [10] and suppression of sebocyte growth [11]. In a large scale of screening of 119 plant extracts for anti-*P. acnes* bacterial activities, five extracts were shown to have a potent anti-biofilm activity against *P. acnes*, and resveratrol was identified as a major active component for eradication of *P. acnes* biofilms [12]. Biofilm is a thin, slimy film of bacteria that adheres to a surface (like a city of bacteria), and responsible for the large majority of infections. Notably, resveratrol demonstrated a sustained antibacterial activity against *P. acnes*, whereas benzoyl peroxide, a commonly used antibacterial treatment for acne, showed a short-term bactericidal response. It is of note that a combination of resveratrol and benzoyl peroxide showed high initial antibacterial activity and sustained bacterial growth inhibition [10]. This combination for treating acne thus warrants future clinical studies.

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FIGURE 2. The chemical structure of resveratrol and the picture of a resveratrol-based cosmeceutical cream. Red grapes are a major natural source of resveratrol.

4. EPIGALLOCATECHIN-3-GALLATE

4.1. Natural Sources and Biological Activities

Green tea is one of the most popular drinks consumed worldwide. Produced mainly in Asian countries from the leaves of the *Camellia sinensis* plant, the potential health benefits of green tea have been widely studied. Drinking green tea has been associated with a reduced risk of various diseases, including cardiovascular disorders [13] and cancer [14], among many others. Green tea extract, under the brand name of Veregen is also a United States Food and Drug Administration (FDA)-approved prescription drug for treating congenital wort [15].

The biological effects of green tea largely result from the green tea polyphenols. Among the green tea polyphenols, EGCG is the most abundant and has received great attention due to its potent biological activities, including anti-inflammatory, antioxidative, and antimicrobial effects [16].

4.2. Cosmeceutical Products

Due to the potential role for skin protection [17, 18], green tea polyphenols, especially EGCG, have recently been increasingly used in various cosmeceutical preparations. **Figure 3** shows the chemical structure of EGCG and the picture of an EGCG-containing cosmeceutical cream.

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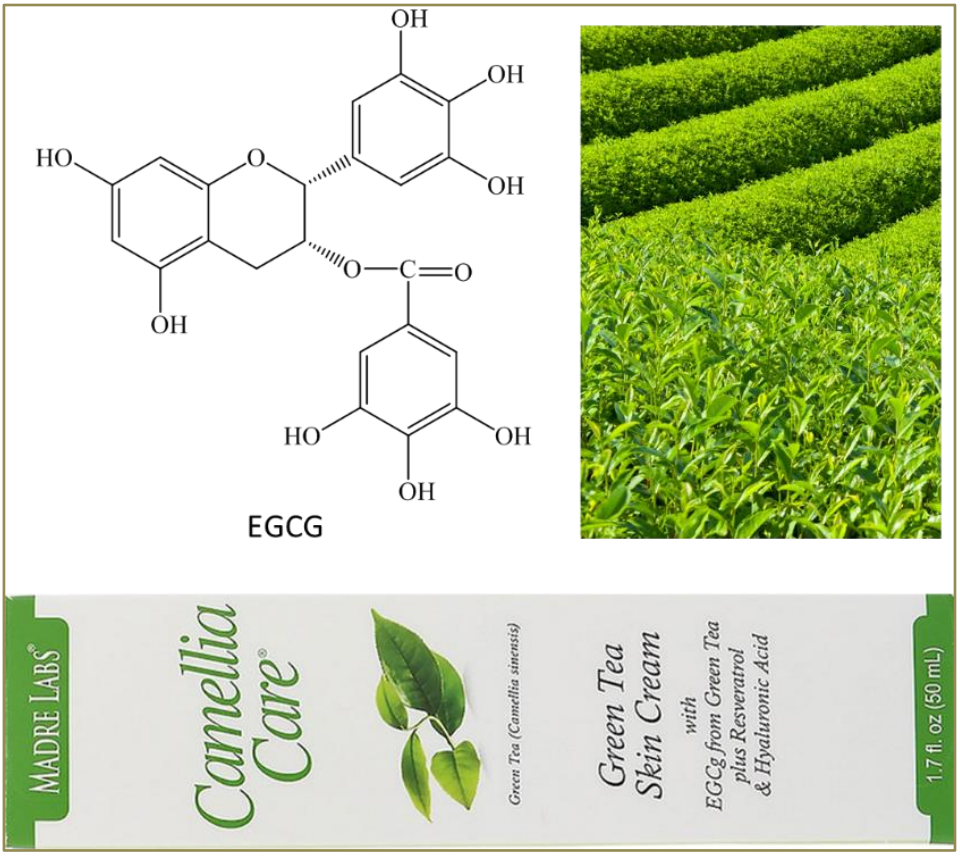

FIGURE 3. The chemical structure of EGCG and the picture of an EGCG-containing cosmeceutical cream. Green tea is the major natural source of EGCG.

4.3. Clinical Evidence

Multiple recent clinical studies have demonstrated an anti-acne efficacy of EGCG and green tea extracts. In a double-blind, randomized split-face trial involving 35 patients with mild-to-moderate acne, topical application of EGCG (1% and 5%; twice daily) for 8 weeks reduced the acne disease severity by 80–90% without causing any significant adverse effects [19]. Can oral intake of EGCG supplements also be effective in improving acne? The answer is yes, based on a double-blind, randomized, placebo-controlled trial on 80 post-adolescent women with moderate-to-severe acne [20]. In the study, the 80 subjects were randomly assigned to receive either 1500 mg of decaffeinated green tea extract (providing 857 mg EGCG) or placebo (cellulose), once daily for 4 weeks. The results showed that green tea extract intake resulted in a significant reduction in inflammatory lesions on the forehead and cheek as compared with the placebo. Compared with the placebo group, the green tea extract-treated group also showed decreased total blood cholesterol. The non-inflammatory acne lesions were, however, not reduced by the treatment [20]. Nevertheless, this trial, for the first time, demonstrated the feasibility of treating inflammatory acne through oral intake of the green tea extract.

4.4. Biological Mechanisms

EGCG acts on multiple pathological processes of acne. For example, it inhibits the growth of *P. acnes* bacteria and suppresses sebum production. It also

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decreases *P. acnes*- and insulin-like growth factor 1 (IGF-1)-induced proinflammatory responses in sebocytes [19, 21]. IGF-1 is a culprit contributing to the development of acne [22].

5. CONCLUSION AND PERSPECTIVES

In conclusion, both resveratrol and EGCG appear to possess anti-acne activities and cosmeceutical preparations containing these natural polyphenols seem to also be effective in treating inflammatory acne based on findings from randomized controlled trials involving a relatively small number of acne patients. Despite of the relatively small sample size of the clinical trials, the well-demonstrated anti-inflammatory properties of both resveratrol and EGCG along with their anti-*P. acnes* activities support the notion that these polyphenols can be promising alternative therapeutic options for acne intervention, especially in those who cannot tolerate conventional drug therapies. Nevertheless, future large-scale clinical studies are warranted to further establish the anti-acne efficacy of resveratrol and EGCG as well as other natural polyphenols.

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