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Examining the Therapeutic Effects of Bioactive Compounds in Orange and Pomegranate for the Management of Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris is the most common inflammatory skin disorder that affects millions of people globally. Various conventional treatments like topical retinoid as-well-as antibiotics are commonly used, but they have many limitations and side effects. But nutraceuticals are gaining much attention for their therapeutic potential in overall skin health and management of skin disorders especially acne.
Objective: The main objective of this review was to examine the therapeutic potential of bioactive compounds present in orange and pomegranate for the management of acne vulgaris, due to their antioxidant, antimicrobial and anti-inflammatory properties.
Materials and Methods: A comprehensive literature review was conducted using databases such as PubMed and Google Scholar. Studies examining the bioactive compounds of orange and pomegranate and their effects on acne-related factors such as inflammation, sebum production, and bacterial growth were included.
Results: Results from the present review demonstrates that pomegranate contains bioactive compounds like ellagic acid and punicalagins, while orange contains flavonoids, hesperidin and vitamin C that have strong antimicrobial, anti-inflammatory, and antioxidant properties against acne-causing bacteria like P. acnes and Staphylococcus aureus.
Conclusion: Nutraceuticals derived from natural food sources like pomegranate and orange demonstrate the therapeutic potential against the acne causing bacteria. Although existing studies suggested their beneficial effects but further clinical trials are still needed in order to fully establish their efficacy as well as to develop the optimized formulations for the oral and topical use against the treatment of acne.

INTRODUCTION

Acne vulgaris is a most common inflammatory skin condition that affects millions of adults globally. Studies have demonstrated that almost 90% of the teenagers have acne, and half of them experience symptoms in adulthood. Results of the recent studies demonstrated an increased prevalence of acne in the children may be due to pubertal onset (1). Most commonly acne appears on parts of the body with the highest amount of sebaceous glands, such as face, back and chest (2).

The importance of acne should not be undervalued because the disease may have significant negative psychosocial consequences for the individuals suffering with acne, such as social withdrawal because of embarrassment, depression as well as diminished self-esteem (3). For most of the individuals, the findings of the safe and effective treatments is a first priority.

Conventional treatments of acne have focused on the reduction of sebum production, targeting bacterial colonization and preventing follicular plugging (4). For this purpose the most common treatment options include such as antibiotics, topical retinoid and other oral medications (5). There are various side effects for these treatments, like topical retinoid may cause many side effects such as skin dryness, irritation, and photosensitivity that limit their use particularly for the individuals having sensitive skin (6). While on the other hand, antibiotics, both oral and topical are also used in order to reduce bacterial load and inflammation but, over the time, there are chance of antibiotic resistance by bacteria especially *P. acnes* that make antibiotics less effective for the long-term management (7).

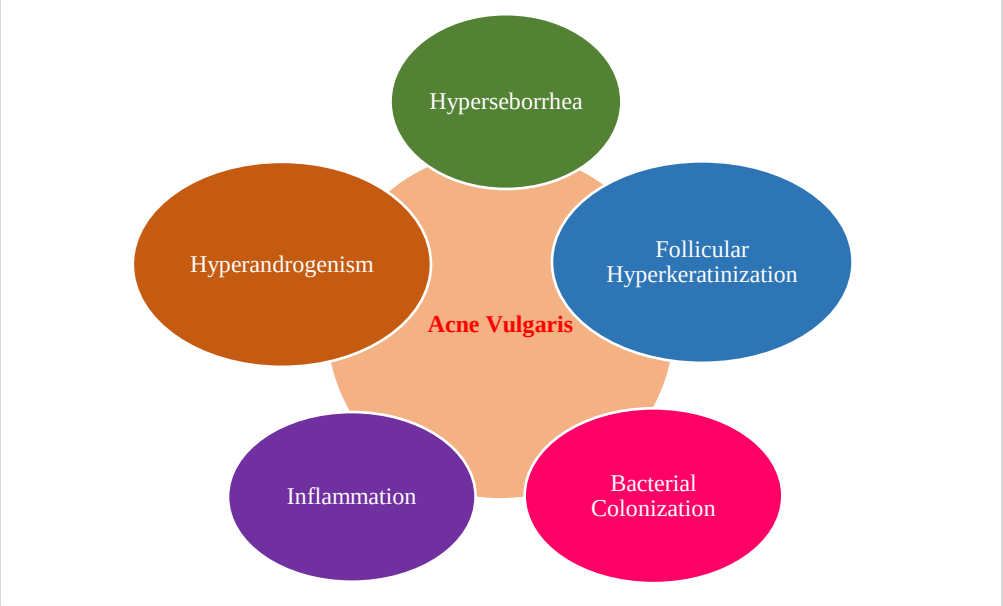
In the recent years, nutraceuticals and natural remedies have gained significant attention in the medical field for the management of diseases, because of their antioxidant, antimicrobial and anti-inflammatory properties (8). Nutraceuticals are the bioactive compounds that are derived from the natural food sources like plants, herbs and fruits that provide greater health benefits beyond their basic nutrition (9). Fruits and herbal remedies have been used for centuries in the traditional medicine, but the recent scientific advancements focused on their actual mechanisms of the active compounds that are basically responsible for their therapeutic potential (10). Among the natural remedies, orange (*Citrus sinensis*) and pomegranate (*Punica granatum*) contain rich amount of bioactive compounds that ultimately exerts antimicrobial, anti-inflammatory, and antioxidant properties, thereby helps to manage the skin disorders especially acne (11, 12).

Factors Contributing to the Onset of Acne Vulgaris

Acne vulgaris is the multifactorial skin disorder that primarily affects the pilosebaceous units that consist of hair follicles, hair shaft as well as its associated sebaceous glands. There are several factors that contribute to the pathophysiology of acne vulgaris, like follicular hyperkeratinization, bacterial colonization, hyperseborrhea (increased sebum production), and inflammation as mention in the Figure 1. Furthermore, hormones can have a greater influence on the exacerbation of acne, especially hyperandrogenism (13).

Figure 1

Factors contributing to the onset and exacerbation of Acne vulgaris



Hyperseborrhea (Increased Sebum Production) and the Onset of Acne Vulgaris

Sebum is basically an oily substance that is secreted by the gland known as sebaceous glands in order to lubricate the skin (14). During the stage of puberty, increased levels of androgens particularly testosterone stimulate the activity of sebaceous gland that ultimately lead to increased sebum (oil) production. This increased production of sebum in the individuals that are predisposed to acne, lead to clogged hair follicles, ultimately provide the ideal environment and condition for the development of acne (15).

Follicular Hyperkeratinization and the Onset of Acne Vulgaris

Follicular hyperkeratinization refers to an abnormal shedding of skin cells known as keratinocytes inside the hair follicles. Usually, these dead cells are shed and replaced with new ones but in the acne prone skin these keratinocytes become sticky and accumulate in the pores, ultimately forms a plug in the hair follicle that blocks the hair follicle, trapping dead cells, sebum as well as other debris inside it, thereby, leading to the formation of whiteheads and blackheads, as well as provide appropriate environment for the proliferation of bacteria that leads to onset of acne (16).

Bacterial Colonization and the Onset of Acne Vulgaris

The trapped dead cells and sebum create an anaerobic environment inside the hair follicle that promotes the growth of *Cutibacterium acnes* (P. acnes), a bacteria that is most commonly found on the skin. It thrives in the sebum rich environment of the skin and release lipases that break down sebum into fatty acids, which irritate the follicular wall and ultimately leads to the inflammation. Moreover, C. acnes also releases the inflammatory mediators like porphyrins that attract the immune cells into the site and thereby, contributing to an inflammatory response (17).

Inflammation and the Onset of Acne Vulgaris

As the *C. acnes* colonizes the blocked follicles, the immune system becomes activated and show its response by sending lymphocytes and neutrophils to the site. Moreover, there is an increased release of inflammatory cytokines like interleukin-1, interleukin-8, and tumor necrosis factor-alpha that ultimately leads to redness, discomfort and swelling associated with the acne lesions. This pro-inflammatory response is majorly responsible to the formation of painful pustules, papules as well as nodules that are more severe manifestations of acne (18).

Therapeutic Potential of Pomegranate in the Management of Acne

Pomegranate (*Punica granatum*) is an ancient fruit that is known due to its therapeutic activities and high nutritive value, making it a best natural remedy for the management of skin diseases. Currently, it has gained greater attention due to its bioactive compounds for the management of acne vulgaris. It is especially rich in antioxidants, antimicrobial compounds and has anti-inflammatory properties that have a crucial role in skin health. Administration of the pomegranate into the treatment of acne has shown promising results in controlling sebum production, reducing acne lesions as well as enhancing the natural defense of skin against the reactive oxygen species and environmental damage (19). It contains different key bioactive compounds such as ellagic acid, punicalagins, and tannins. All of these bio-active compounds exhibits a unique mechanisms that contribute to the management of acne by its anti-inflammatory, antioxidative as well as antimicrobial effects as mentioned in the Figure 2.

Role of Punicalagins in the Management of Acne

Punicalagins are strong antioxidants that are primarily present in the juice as well as peel of pomegranate. As a polyphenolic compounds, punicalagins have strong property for neutralizing free radicals, thereby play an important role to prevent skin cell damage and inflammation (20). Moreover, punicalagins also have an important role to protect and stabilize natural barrier of skin that is essential for the individuals having acne-prone skin. Because a compromised skin barrier often results in increased loss of moisture contents as well as vulnerability to the environmental irritants that can further exacerbate acne and inflammation.

Thereby, these punicalagins helps the skin to retain moisture level and protect from environmental irritants (21). Moreover, the punicalagins also increase the natural repair processes of the skin thereby, enhancing the faster healing of acne lesions and reducing the risk of post inflammatory pigmentation of skin (22).

Role of Ellagic Acid in the Management of Acne

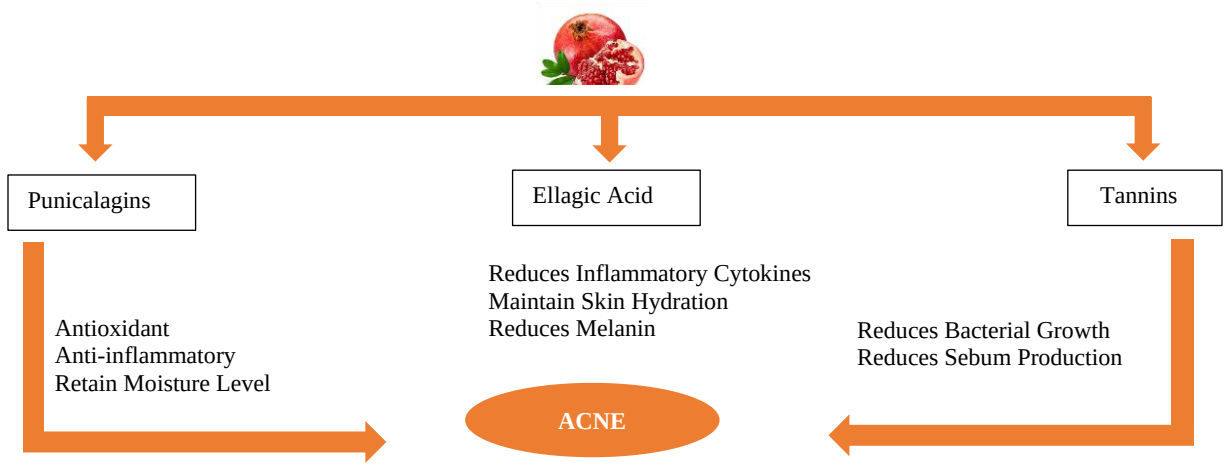
Ellagic acid is a powerful polyphenolic compound that is found in pomegranate and it is recognized for its extensive antioxidative and anti-inflammatory effects that increases its effectiveness against acne as well as promoting the skin health. Ellagic acid also inhibits the expression of inflammatory cytokines like interleukin-1 beta as well as tumor necrosis factor-alpha (TNF-α). These pro-inflammatory cytokines are elevated in the inflamed acne lesions that contribute to swelling, redness and pain. Therefore, by down-regulating these pro-inflammatory mediators, ellagic acid helps to reduce the severity of inflammation and prevent the further irritation in the acne lesions (23).

Ellagic acid also acts as a strong antioxidant that protect the skin cells from oxidative damage caused by free radicals by preventing the damage to cellular structures, including proteins, DNA and lipids that can accelerate the skin aging process. This protective effect of ellagic acid also helps the natural barrier of skin to reduce trans-epidermal water loss and maintain hydration (24). Furthermore, ellagic acid has a great potential to inhibit the production of melanin that can prevent the post-inflammatory hyperpigmentation. Inflammation induced by acne can trigger melanogenesis that can lead to uneven skin tone and dark spots after the acne heals. So, by interacting the activity of melanocyte and tyrosinase enzyme an ellagic acid helps to reduce the acne scars and maintain an even skin tone as mentioned in the Figure 2 (25).

Role of Tannins in the Management of Acne

Tannins are the class of polyphenolic compounds that are present in pomegranate. These are known for their astringent, antimicrobial as well as anti-inflammatory effects that makes them highly effective in the management of acne by inhibiting the activity of *Propionibacterium acnes*, a bacteria that colonizes the hair follicles that significantly contributes to the inflammation in the acne (26). Tannins also works to neutralize the *C. acnes* by reducing the bacterial growth and lowering the risk of secondary infections. Furthermore, tannins also exhibit the strong astringent effect that play an important role in the management of acne by tightening the pores of skin and reducing the sebum production as mentioned in the Figure 2. Moreover, tannins also acts as an anti-inflammatory and antioxidative agent that helps in the management of acne (27).

Figure 2
Therapeutic Potential of Pomegranate in the Management of Acne



Therapeutic Potential of Orange in the Management of Acne

In Sanskrit, the word "orange" comes from the word "naranga," which means "orange tree." The bitter orange is categorized as Citrus aurantium, while the sweet orange (Citrus sinensis) is the most commonly consumed citrus species worldwide today. According to genetic research, sweet orange is a hybrid that is made up of roughly 75% mandarin (Citrus reticulata) and 25% pomelo (Citrus maxima) (28). Oranges are a popular fruit that can be eaten whole, peeled, or juiced. They are also a cheap way to get important nutrients like vitamins C, A, and B, as well as minerals like calcium, phosphorus, and potassium. They are also high in dietary fiber and a variety of phytochemicals, including carotenoids, phenolic acids, triterpenes, and flavonoids (29). Strong antioxidants such as flavonoids (especially hesperetin and naringenin as glycosides), carotenoids (xanthophylls, cryptoxanthins, and carotenes), and vitamin C are what make orange juice (OJ) so valuable.

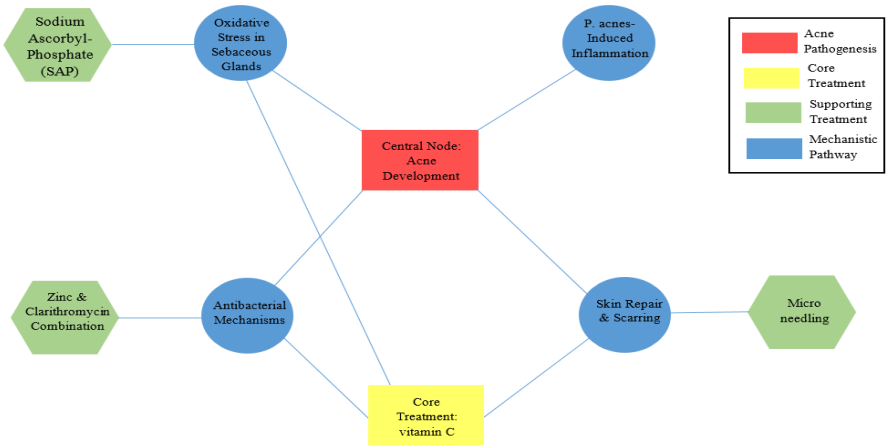
Role of Vitamin C in the Management of Acne

Acne development is closely associated with oxidative stress, particularly within the sebaceous glands where lipids are vulnerable to peroxidation**.** Vitamin C acts as a powerful antioxidant, capable of neutralizing reactive oxygen species (ROS) that would otherwise intensify inflammation and worsen acne lesions. Through its electron-donating capacity, Vitamin C stabilizes free radicals, protecting skin lipids from oxidative damage and thereby helping to prevent the formation of comedones, which are the precursors to acne (30). A stable derivative of Vitamin C, sodium ascorbyl phosphate (SAP)**,** has been shown to prevent UVA-induced lipid peroxidation within the skin, which further reduces the risk of pore blockages and bacterial growth on the skin's surface. By lowering oxidative stress markers, SAP indirectly minimizes the conditions that allow acne-causing bacteria, such as Propionibacterium acnes (P. acnes)**,** to thrive (31). This underscores the role of Vitamin C not only as an antioxidant but also as a preventive agent against the inflammatory responses commonly triggered by acne**.** P. acnes plays an active pro-inflammatory role in acne development by interacting with keratinocytes and sebaceous glands within the pilosebaceous unit, thus leading to the inflammation and formation of acne (32). Studies indicate that a combination of zinc, clarithromycin, and Vitamin C possesses antibacterial effects against clarithromycin-resistant strains of P. acnes**.**

Furthermore, Vitamin C combined with micro needling has shown promising results in treating acne scars. This approach enhances skin firmness and smoothness and reduces post-inflammatory pigmentation, making it a dual-action solution for both acne and its scarring (33). Vitamin C's role in promoting collagen synthesis also supports skin repair, contributing to improved skin texture and pigmentation post-acne.

Figure 3

Role of Vitamin C in the Management of Acne



Role of Carotenoids in the Management of Acne

Carotenoids are non-polar, fat-soluble compounds from the terpene family that contain a polyene chain ending in cyclohexane rings or aliphatic isoprenoid groups, stabilized by a highly delocalized π-electron system (34). The main forms of vitamin A, retinol (vitamin A1) and dehydroretinol (vitamin A2), can be metabolized in the skin into retinal and then retinoic acid. Retinoic acid is widely used in dermatology for its keratolytic and anti-inflammatory effects, particularly in treating acne and related inflammatory skin conditions. Alongside reducing inflammation and promoting skin cell turnover, retinoic acid offers antioxidant benefits that help protect the skin (35).

Role of Flavonoids in the Management of Acne

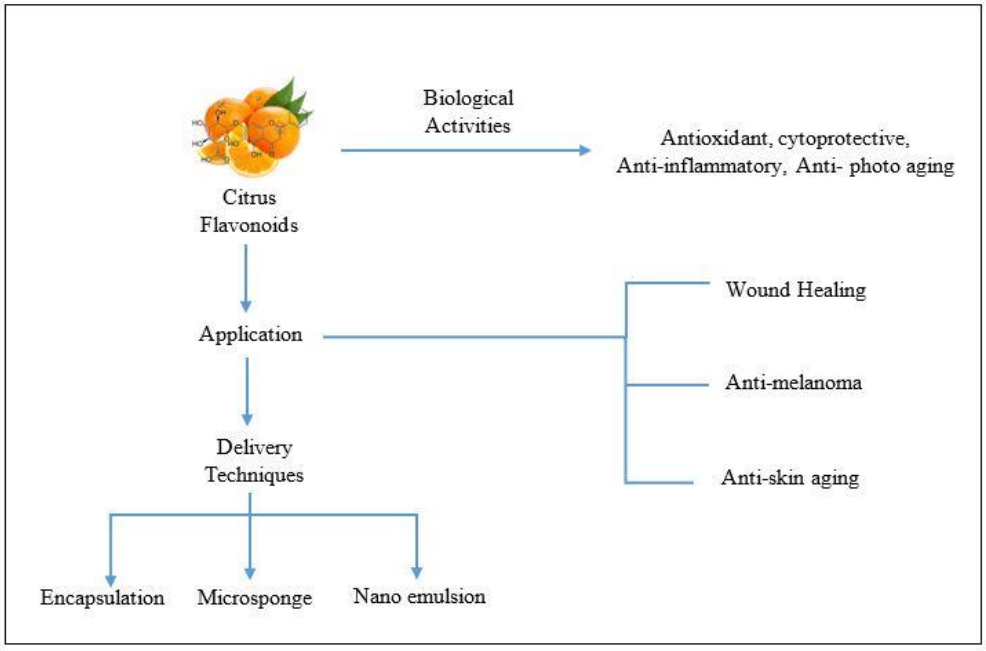
Numerous dietary flavonoids, including hesperidin, hesperetin, naringin, naringenin, quercetin, rutin, diosmin, diosmetin, kaempferol, myricetin, nobiletin, tangeretin, and others, are found in citrus fruits. These aromatic bioactive compounds and polyphenols are secondary metabolites found in plants and contribute to health promotion by participating in various biochemical processes in the human body, particularly benefiting skin health in cases of pigmentation, photoaging, aging, and general skin maintenance (36).

Flavonoids, natural compounds with potent antioxidant properties, are gaining attention for their benefits in managing acne. These natural products are promising for both prevention and treatment due to their broad pharmacological activities (37). Specifically, flavonoids' antioxidant effects help neutralize free radicals and protect the skin from oxidative stress that worsens acne (38). Flavonoids such as quercetin and licorice extracts have shown particular effectiveness in reducing inflammatory responses triggered by *Propionibacterium acnes*, the primary bacteria associated with acne (39).

These plant-based compounds are widely used in skincare formulations, typically in mixtures containing aglycones and lipophilic glycosides, a composition that enhances their antioxidant capabilities and allows flavonoids to neutralize nearly all free radical types (40). Their high affinity for singlet oxygen and ability to reduce oxidative stress make them effective in combating inflammation that exacerbates acne. By inhibiting various ROS-producing factors, flavonoids support clearer, healthier skin (41).

Figure 4

Therapeutic Potential of Orange in the Management of Acne



Role of Hesperidin in the Management of Acne

The bacterium that is closely linked to acne, Propionibacterium acnes (P. acnes), thrives in the low oxygen environment of blocked sebaceous glands (42). There, it releases inflammatory mediators and enzymes that aid in the development of acne lesions. Several skin pathogens, including P. acnes, are susceptible to the antimicrobial effects of hesperidin. Hesperidin lowers the bacterial burden in the pilosebaceous units by preventing bacterial colonization and the subsequent formation of biofilms, which in turn lessens the severity of acne outbreaks. The concepts of oxidative stress and skin aging are deeply interconnected, with oxidative stress playing a pivotal role in skin health (43). Oxidative stress in cutaneous tissue results in the degradation of the extracellular matrix (ECM) by matrix metalloproteinases (MMPs) and enzymes like elastase, leading to the breakdown of structural proteins such as collagen and elastin (44). MMPs typically assist in ECM remodeling, but when overexpressed under oxidative conditions, they accelerate tissue degradation, promoting damage that contributes to skin conditions like acne. Oxidative stress also drives the production of reactive oxygen species (ROS), which further damage cellular components by causing DNA and mitochondrial injury, lipid peroxidation, and breakdown of cell adhesion and basement membrane structures, ultimately compromising the skin barrier (45). Since ROS production impairs the skin barrier, it can lead to issues like moisture loss, inflammation, and susceptibility to acne. Therefore, compounds that target oxidative stress mechanisms hold potential for acne management by regulating intracellular pathways related to ROS and improving the skin's defense mechanisms. For instance, hesperidin has been shown to target MMPs by enhancing the expression of tissue inhibitors of metalloproteinase (TIMPs), offering a regulatory effect against oxidative damage. Additionally, hesperidin may protect against ROS by directly neutralizing them, inducing antioxidant enzymes, or inhibiting oxidases (46).

CONCLUSION

This review concludes that bioactive compounds from the natural sources like pomegranate and orange demonstrates great potential in the management of acne. Pomegranate contains the punicalagins, ellagic acid, and tannins that have strong anti-inflammatory, antioxidant, and antimicrobial properties, thereby reducing the acne-causing bacteria and soothing the inflamed skin. While orange is rich in flavonoids like hesperidin as well as rich in Vitamin C that contributes to acne control by neutralizing the reactive oxygen species thereby reducing oxidative stress, and improving the texture of skin. Both these natural compounds can address bacterial colonization, acne-related inflammation as well as oxidative damage.

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