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Submission date: 13-Jan-2023 02:00PM (UTC+0700)
Submission ID: 1992179014
File name: 23._Agussalim_Bukhari-Dwiana_Savitri.pdf (412.71K)
Word count: 6210
Character count: 35468

Annals of Medicine and Surgery 84 (2022) 104868

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Review

Active compounds in kepok banana peel as anti-inflammatory in acne vulgaris: Review article

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ARTICLE INFO

Keywords:
Kepok banana peel
Anti-inflammatory
Acne vulgaris

ABSTRACT

Background: Acne vulgaris (AV) is a chronic inflammatory skin condition affecting the pilosebaceous units characterized by recurrent comedones, erythematous papules and pustules. The disease is benign however may produce scarring, erythema, and hyperpigmentation resulting in physical and psychological problems. Conventional therapy may reduce the symptoms of AV nevertheless, has a possibility of resistance, unwanted side effects, and has high cost. Thus, utilizing natural remedies may be a useful.

Methods: The data in this study were collect by search the keyword combinations of medical subject heading (mesh) of "inhibition", "antimicrobial", "banana peel", "acne vulgaris" and "antiinflammation" and relevant reference lists were manually searched in PubMed, EMBRASE and Scopus database. All relevant articles in data base above were included and narratively discussed in this review article.

Objective: To discuss the bioactive potential of banana peel as an inflammatory modulator in acne vulgaris.

Results: Banana peel contains many bioactive compounds, particularly phenolic and non-phenolic antioxidants (ascorbic acid, carotene, and cyanidin) which are pivotal in removing inflammatory products by inhibiting reactive oxygen species (ROS), protecting protease inhibitors from oxidative damage, and preventing fibroblasts degradation. Banana peel also contains anti-inflammatory agents such as trigonelline which inhibits bacterial enzymes and nucleic acid synthesis; isovanillic acid which suppresses TNF-α production; and ferulic acid which inhibits the production of proinflammatory signaling and cytokines.

Conclusion: Banana peel contains many bioactive compounds which demonstrate anti-inflammatory properties through several processes of the inflammatory pathway. However further research is needed to confirm this finding.

1. Introduction

Acne vulgaris (AV) is a chronic inflammatory skin disease of the pilosebaceous units (sebaceous glands and hair follicles) on the face, neck, trunk, or proximal upper extremities. This disorder is characterized by the development of chronic or recurrent comedones, erythematous papules, and pustules [1]. The degree of severity is in the form of open or closed comedones (non-inflammatory) lesions followed by pustules and papules (inflammation), and residual pathology in the form of nodules and cysts [2,3]. AV is a disease that is widespread in all races, ethnicities, and cultures. Although it is benign, self-limiting and not life-threatening, in chronic inflammation cases it will trigger symptoms of scars, erythema, and hyperpigmentation that trigger physical and psychological problems [1]. Psychological problems can be depression, anxiety [4], and unemployment [5].

Conventional topical therapy refers to the AV type and is associated with symptoms. Therapies applied include antibacterial agents, decreased sebum secretion, triggers of cellular turnover, anti-

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https://doi.org/10.1016/j.amsu.2022.104868
Received 12 August 2022; Received in revised form 4 October 2022; Accepted 6 November 2022
Available online 12 November 2022

inflammatory agents. In severe cases the clinician will give oral antibiotics, retinoids, and hormonal therapy [6]. Conventional therapy still has high costs and leaves side effects, in the form of resistance [7,8]. This leads to a new approach in the form of utilizing natural or herbal resources.

Previous study has shown that some herbs can be used as antimicrobial [9–12], antifungal [13], anti-inflammatory [10,11,14–18], antidiabetic [19], antihipertensive [20], anti-sedative [21,22], and reducing oxidative stress after traumatic brain injury [23–25].

Banana (Musa spp.) is one of the fruits that is widely distributed and consumed throughout the world. Bananas have an attractive nutritional value, taste and are a popular fruit in industrialized countries. This plant is widely grown in tropical and subtropical regions and is centered in its original area, namely Southeast Asia and the Western Pacific [42]. This plant is found in more than 130 countries as a food source and contributes to 17% of world fruit production [27,28]. Banana flesh is wrapped by a yellow skin. When ripe, bananas have a light yellow skin with brown specks. Until now, there have not been many studies in terms of nutrition, pharmacy and its bioactive potential for banana peels [29]. Several active compounds from ripe and unripe banana peels include fiber, pectin, phytosterols, phenolics, biogenic amines, and carotenoids. The latter four exhibit antioxidant properties, thus producing health benefits [30,31]. However, there are limited studies that demonstrate a direct association between banana peel and acne vulgaris. Therefore, this paper aims to discuss the bioactive potential of banana peel as an inflammatory modulator in acne vulgaris.

2. Methods

Then data in this study were collect by search the keyword of medical subject headings (MeSH) of "inhibition", "antimicrobial", "banana peel", "acne vulgaris", and "antiinflammation" and relevant reference list were manually search in PubMed, EMBRASE and Scopus database. All relevant articles in data base above were included and narratively discussed in this review articles [27,28].

3. Body of article

3.1. Epidemiology of acne vulgaris

There is little to no universal standard on the minimal criteria of acne vulgaris diagnosis. Different studies employ different criteria and therefore becomes difficult to compare, compile, and extrapolate their results. The prevalence estimates are also influenced by various factors such as the country where the data was gathered from and the sample size. This creates stark variation across different studies [32]. A study conducted in Germany found the prevalence estimate of 26.8%, whilst a study in Brazil found the prevalence estimate to be 96% [33]. According to the Global Burden of Disease Study 2010, acne vulgaris is the eight most common skin disorder. The prevalence estimate reached 9.38% globally. The study also mentioned the estimated prevalence of 8.96% in males and 9.81% in females [34]. In contrast, a systematic review revealed that the pooled odds ratio for males is 1,07 (95%CI = 1,97–2, 83) with reference to females. The prevalence was also found to increase with age. Teenagers have the highest incidence and pre-pubertal children have the lowest. During the young adult years, the prevalence declines gradually as the age increases. Aside from sex and age, family history and BMI are also proven to bear significant association with acne vulgaris. There is a strong association between acne vulgaris and having parents with the history of acne vulgaris. The pooled odds ratio is 2,91 (95%CI = 2,58–3,28). Obesity is also proven to be a risk factor of acne vulgaris. According to the pooled odds ratio, An obese patient is estimated 2,36 (95%CI = 1,97–2,83) times to have acne vulgaris compared to normal/underweight patient. The association between acne vulgaris and smoking, dietary factors, and the severity of acne was found to be inconsistent across multiple studies [32].

3.2. Pathogenesis of acne vulgaris

Acne vulgaris most commonly affects pilosebaceous units of the face, chest, upper arms, and upper back due to their high density of sebaceous glands. There are four main sequential factors leading to acne vulgaris, namely increased sebum production, followed by irregular follicular desquamation, proliferation of *C. acnes*, and inflammation [35–37].

Sebum production is proportional to the severity of the acne lesions. Androgen hormones increase sebum production since the increase in androgens is not accompanied with an increase in the sensitivity of androgen receptors [38]. Sebum production is also influenced by growth hormone. IGF-1 reduces the intracellular level of nuclear metabolic forkhead box class O transcription factor 1 which leads to activation of the mammalian target of rapamycin complex 1 (mTORC1). mTORC1 is associated with cell proliferation and metabolism, in this case, the hyperproliferation of sebaceous gland and keratinocyte. IGF-1 also increases androgen levels and endogenous IGF-1, thereby creating a positive feedback loop [39].

Androgens also cause hyperproliferation of the keratinocytes which occlude the follicles and cause microcomedones to form. Comedogenesis requires hyperproliferation of the keratinocyte and subsequent gathering of desquamated corneocytes in the follicle. Microcomedone fills the follicle with lipids and microfilaments which can turn into non-inflammatory comedones or inflammatory acne lesions. There are open comedones or blackheads and closed comedones or whiteheads. Blackheads contain desquamated keratinocytes and sebum. Whiteheads appear as whitish bumps beneath the skin, which may rupture to the surrounding tissue [35].

Comedones are the suitable site for microbial proliferation. The three normal microflora of the sebaceous follicles are coagulase-negative staphylococci, anaerobic diphtheroids, and lipophilic yeasts. Yeasts rarely partake in the pathogenesis of acne vulgaris. Coagulase-negative staphylococci elicits harmless antibody responses in comparison to *C. acnes*. *S. epidermidis* is an aerobic organism which grows superficially instead of deeply in the anaerobic infra-infundibulum where inflammation takes place. On the contrary, *C. acnes* is an anaerobic organism which colonizes the sebaceous follicles to obtain nutritious lipids. The response of immune system towards the bacteria trigger the formation of papules, pustules, and even cysts and nodules in severe cases [32,40].

3.3. C. acnes as initiator

A human skin commensal bacterium, *Propionebactrium acnes* (*P. acnes*), is now called *Cutibacterium acnes* (*C. acnes*) based on a new taxonomy. *C. acnes* is a commensal and predominant Gram-positive bacteria (>60% of total bacteria) in the skin. Almost everyone is a host of this bacterium, with a density of 10^5-10^6/cm^2 accounting for half of the total microbiome [41]. *C. acnes* is believed to play an important role in the pathogenesis of the development of AV lesions [42]. *C. acnes* induces sebaceous triglyceride metabolism, glycerol consumption, and release of free fatty acids, neutrophils, and complement attractants. *C. acnes* contributes to inflammation through monocyte induction of pro-inflammatory cytokine secretion. In vitro, *C. acnes* also triggers the secretion of antimicrobial peptides and cytokines from keratinocytes [43].

Innate immunity is the first line of defense against pathogens (pathogen-associated molecular pattern) and danger (danger-associated molecular pattern). Responses to PAMPs or DAMPs are mediated by pattern recognition receptors, such as Nod like receptors (NLRP1, NLRP2, NLRC4, and AIM2). These receptors will respond in the form of formation of inflammasomes that control the activation and secretion of pro-inflammatory cytokines [44]. *C. acnes* can activate the NLRP3 inflammasome pathway leading to an increase in IL-1β levels. Furthermore, *C. acnes* will be recognized by pattern recognition receptors, including TLR2 and TLR4 to elicit an immune response against bacteria. TLR2 activation triggers the release of cytokines and attracts

inflammatory cells toward the lesion. This event will activate infiltrating cells and release pro-inflammatory cytokines namely IL-6, TNF-α, IL-12, IL-8, and IL-1β. In recognition of *C. acnes*, TLRs can activate cellular components including TNF-α and IL-1A, then activate the chemokines IL-8 and IL-10, finally activating downstream components of inflammation. IL1A activity is also modulated by IL1RN [45,46].

TNF-α will interact with its receptor, TNFR2 to activate the inflammatory signaling cascade. The cascade will activate MAPKs, including MAPK11 which upregulates the expression of pro-inflammatory mediators, and also activates matrix MMPs, including MMP-2 to trigger tissue remodeling. MMP activity is regulated by TIMPs, altering the balance of MMP and TIMP activity which also contributes to acne development. IL-6 (stimulated by IL17A, IL17F, and ACE) plays a role in modulating host defense and inflammation. On the other hand, TGF-β not only plays a role in the synthesis of lipid sebocytes, but also controls the immune response against *C. acnes* [45,46].

3.4. Inflammation

Inflammation is required for host defense as a response against invading pathogens, toxic compounds, or noxious endogenous signals. On the other hand, the body's failure to stop this process will trigger tissue or organ damage [47]. Inflammation in acne vulgaris is a consequence of the interaction between *C. acnes* and innate immunity. This inflammation is characterized by the production of cytokines, chemokines, and antimicrobial peptides from the epidermis and immune cells. The effects of *C. acnes* infection, hyperkeratinization, and activation of innate immunity are prolongation of inflammation that triggers the occurrence of severe acne lesions [48].

There are different strains of *C. acnes* with varying resistance profiles which colonize different pilosebaceous units. The bacteria induce inflammation after being detected with toll-like receptors in macrophages and keratinocytes [49]. As *C. acnes* is detected by the immune system, the inflammatory process begins. The immune system, particularly from the lymphocytes, neutrophils, and macrophages, releases chemostatic factors. These molecules trigger follicular damage, rupture, as well as leakage of not just bacteria but also lipids and fatty acids into the surrounding dermis. As a result, inflammatory lesions such as nodules, pustules, papules, and cyst emerge. There are also reactive oxygen species released by neutrophils which damage the follicular epithelium and aggravate the inflammatory process [50].

3.5. Antimicrobial peptides

Antimicrobial peptides are usually small (<20 kDa), positively charged amphiphilic molecules with a linear -helix or -sheet motif. Antimicrobial peptides are important effectors of the innate immune system and provide the first line of defense against microorganisms [51,52]. In human skin, antimicrobial peptides are produced by keratinocytes, neutrophils, sebocytes, or sweat glands. There is a correlation between disease severity and the amount of antimicrobial peptide production [53].

Antimicrobial peptides are amphipathic and cationic so they can interact with bacterial anionic membranes to trigger membranolysis (Wimley et al., 2010). In addition to membranolysis, antimicrobial peptides are also anti-inflammatory, bind to lipopolysaccharide/and/or lipoteichoic acid, and trigger bacterial agglutination [54–56]. Compared to conventional antibiotics, antimicrobial peptides are able to modulate the host immune response and are less likely to induce short-term bacterial resistance due to different actions [57]. Thus, antimicrobial peptides can be candidates for AV through direct bacterial killing and inhibition of Toll-like receptors in NF-κβ activation [58].

Human β-defensins are found primarily in epithelial cells and a number of sites in the body. The human β-defensin gene was found at constitutively low levels in epithelial cells. This transcription is induced by various factors, namely microbes and cytokines. There is ample evidence that pro-inflammatory cytokines (IL-1β and TNF-α) and bacterial lipopolysaccharides can upregulate human -defensins. Research on the Han population in China found that there was a significant difference in the DEFB1 C-44G and G-20 A polymorphisms between acne vulgaris cases compared to controls ($p < 0.05$). Alleles C-44G and G-20 A are underexpressed in acne vulgaris, which correlates with a lower risk of acne vulgaris in Han Chinese patients [59].

Two antimicrobial peptides from frog skin, namely [D4k]ascaphin-8 and [T5k]temporin-Dra can inhibit the growth of P. acnes and the release of cytokines and even trigger the production of anti-inflammatory cytokines [60]. Antimicrobial peptide HPA3NT3 as a synthetic peptide derived from Helicobacter pylori is antimicrobial against *P. acnes* and can block *P. acnes*-induced inflammation [61]. The antimicrobial peptide CEN1Hc-Br derived from green sea urchin is antimicrobial and inhibits the induction of toll-like receptor-2 expression by *P. acnes*. In addition, CEN1Hc-Br is also able to downregulate inflammatory cytokines in vitro and in vivo [62]. Bombinin is an antimicrobial peptide from the skin secretions of Bombina species [63]. BLP-7 contains 27 amino acids, including 4 cationic amino acids, namely Lis, Arg and His and 18 hydrophobic amino acids. It appears that the antimicrobial peptide properties of BLP-7 are via hydrophobicity. BLP-7 inhibits the expression of Il-8 and GM-CSF in NHEKs [42].

3.6. Active compound in kepok banana peels as anti-inflammation in acne vulgaris

Despite occupying 40% of the total weight, banana peels are often discarded. Banana peel has only been used as animal feed, which is not economically and environmentally friendly [64]. In many Asian countries, banana peel is used for traditional medicine and cosmetic purposes such as astringent [65,66]. Banana peel contains plenty of bioactive compounds. According to a study on *Musa sapientum Linn.* (*Musaceae*), the fresh ripe peel contains NO inhibitory activity without any antioxidant effect. However, the decoction from the unripe peel demonstrated significant antioxidant activity and high phenolic content. The study further shows that the antioxidant activity is correlated to the total phenolic content [65].

Phenolic is one of the active compounds from banana peel. The phenolic content of banana peel compounds is 35 mg equivalent of gallic acid/g extract and 428 mg/g equivalent of quercetin [67]. Gallocatechin is another phenolic antioxidant identified in banana peel. It has higher amount in the peel (158 mg/100 g of dry weight) than in the pulp (29.6 mg/100 g of dry weight) according to studies on *M. cavendishii Lamb* [68,69]. Other phenolics found in banana peel include catecholamines, flavanones, flavonols, tocopherols [70].

Non-phenolic antioxidant compounds in banana peel are ascorbic acid, carotene, and cyanidin. Banana peel contains higher carotenoid values, particularly *trans*-beta-carotene, *trans*-alfa-carotene, and *cis*-beta-carotene which are respectively 174.87 ± 7.86 μg/g dry weight), 164.87 ± 10.51 μg/g dry weight, and 92.21 ± 5.37 μg/g dry weight [68]. On another hand, sterol compounds from banana peels include stigmasterol, -sitosterol, and campesterol. The tripenic alcohols from banana peels include cycloartenol, cycloeucalenol, and 24-methylene cyancartanol. Sterols and triphenic alcohols are lipids without a phenolic ring and without antioxidant activity [71]. Stigmasterol can inhibit the production of pro-inflammatory mediators (TNF-a, IL-6, IL-1b, iNOS, and COX-2) and increase the expression of anti-inflammatory mediators (IL-10) [72]. Antioxidants play an important role in the removal of inflammatory products by working against proteases as well as reactive oxygen species (ROS). Antioxidants also protect protease inhibitors from oxidative damage. Antioxidants also prevent fibroblasts and other cells degradation caused by ROS [68].

An experimental study on rats proved that oral banana peel extract is associated with lower concentrations of hydroperoxides, peroxidation products (MDA), and conjugated dienes. Simultaneously, rats treated with banana peel showed increased catalase and superoxide dismutase

activities. This is also followed by reduced concentration of glutathione [68].

LC-HRMS analysis on the ethanolic extract of Kepok banana peel found compounds of trigonelline, isovanillic acid, vanillin, ferulic acid, 3-methoxyflavone, rutin, and salsolinol. Trigonelline is an alkaloid found in the ethanolite extract of the Kepok banana peel [73]. Although nothing has been proven directly on acne vulgaris, various studies have proven the role of trigonelline as an anti-inflammatory in other diseases. The anti-inflammatory trigonelline pathway is through depression of nuclear factor kappa beta (NF-kβ), depression of TLR4, and inhibition of pro-inflammatory cytokine production [73]. Trigoneline as an alkaloid is also antibacterial through the mechanism of inhibiting nucleic acid synthesis through dihydrofolate reductase or topoisomerase activity, inhibition of cell division protein (FtsZ), inhibition of bacterial enzymes, and disruption of the outer membrane and bacterial cytoplasmic membrane integrity [74]. Isovanillic acid can suppress the production of TNF-α due to induction by LPS [75]. Ferulic acid is an organic acid. Ferulic acid can restore the production of inflammatory cytokines, suppress the production of proinflammatory cytokine mRNA, inhibit Ikβ degradation and phosphorylation of NF-kβ p65 due to LPS induction [76,77].

A study on 45 female Indonesian adolescents was carried out to determine the efficacy of banana peel on acne vulgaris in 2018. The research found that before the application, the prevalence of mild, moderate, and severe acne vulgaris was 62.2% (28), 33.3% (15), 4.4% (2) respectively among the subjects. The ripe banana peel was rubbed on the acne and left for 30 min to an hour. The process was repeated every day for 7 days. After the application of banana peel, the prevalence of mild, moderate, and severe acne vulgaris became 62.2% (28), 33.3% (15), 4.4% (2) respectively. Furthermore, the study also found that 57.9% of the samples who used to have moderate acne vulgaris recede to mild acne vulgaris. Wilcoxon signed rank proved significant difference (p value = 0.016) [66].

3.7. Implication

The implications of this potential point to the need for in vivo studies. The active compounds from banana peel have broad pharmacological potential, as anti-inflammatory and antibacterial that can be used to inhibit the development of acne vulgaris.

4. Conclusion

Banana peel contains many bioactive compounds, particularly phenolic and non-phenolic antioxidants such as ascorbic acid, carotene, and cyanidin. Antioxidants play an important role in the removal of inflammatory products by inhibiting reactive oxygen species (ROS), protecting protease inhibitors from oxidative damage, and preventing fibroblasts degradation [68]. Banana peel also contains anti-inflammatory agents called trigonelline, isovanillic acid, and ferulic acid [73]. Trigonelline inhibits bacterial enzymes and nucleic acid synthesis [74]. Isovanillic acid suppresses TNF-α production due to induction by LPS [75]. Ferulic acid suppresses proinflammatory signaling and cytokine production [76,77]. An experimental study on the application of banana peel on 45 female subjects found significant alteration of acne vulgaris severity [66]. However further research is needed to confirm this finding.

Ethical approval

None.

Sources of funding

None.

Author contribution

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Registration of research studies

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Unique Identifying number or registration ID:0000-0002-8456420 3 Hyperlink to your specific registration (must be publicly accessible and will be checked):-

Guarantor

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Consent

None.

Declaration of competing interest

The authors declares there is no conflict of interest.

Abbreviations

	acne vulgaris
IGF-1	Insulin-like growth factor 1
mTORC1	mammalian target of rapamycin complex 1
IL	Interleukin
TNF	Tumor necrosis factor
κβ	Nuclear factor kappa beta
PAMPs	Pathogen-associated molecular patterns
DAMPs	Danger-associated molecular patterns
NLRP	Nod like receptors
TLR	Toll-like receptors
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
-7	Bombinin-like peptide 7
COX-2	Cyclooxygenase-2
mRNA	Messenger ribonucleic acid
LPS	Lipopolysaccharide

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