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Comprehensive review of the skin use of bakuchiol: physicochemical properties, sources, bioactivities, nanotechnology delivery systems, regulatory and toxicological concerns

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Abstract Bakuchiol is a meroterpene that has recently aroused great interest in the cosmetic and pharmaceutical industries. Its main source is the seeds of *Psoralea corylifolia,* a medicinal plant native to Asia, despite having a wide geographical distribution. However, this medicinal herb faces endangerment due to low seed germination rates and high seedling mortality. In this context, this review article highlights studies that have focused on describing plant regeneration from root fragments. Subsequently, given its morphological similarity to other species, a technique that can be used to verify the authenticity of the plant and prevent counterfeiting is also mentioned and explored. Additionally, a "green" extraction method for obtaining bakuchiol is presented, and the possibility of obtaining bakuchiol through chemical synthesis routes is also explored. Furthermore, we provide an exhaustive description of bakuchiol's wide range of biological activities, with particular relevance to the skin. The main skin bioactivities of bakuchiol include antifungal, antibacterial, antioxidant, anti-inflammatory, antiaging, depigmenting, and anticancer. However, the particular physicochemical properties of bakuchiol require and benefit from the development of innovative skin delivery systems that allow its encapsulation. These include micro- and nano-sized systems for therapeutic and cosmetic applications, which are also carefully described in this review article. Finally, regulatory issues, metabolic considerations, and toxicological concerns related to the use of bakuchiol in cosmetic and dermopharmaceutical formulations will be addressed, relating not only to the user but also to the environment.

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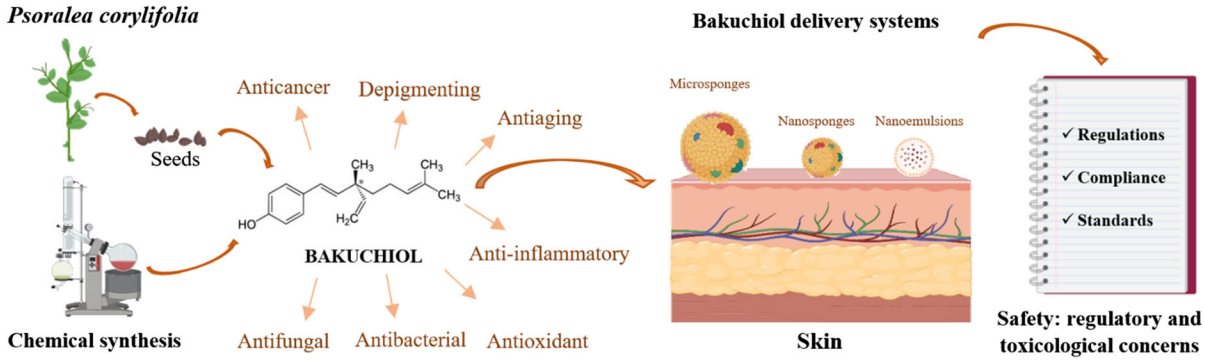
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Graphical abstract



Keywords Bakuchiol · Delivery system · Nanotechnology · Regulatory · Skin bioactivity · Toxicology

Abbreviations

AQP3	Aquaporin 3
BAK	Bakuchiol
β-CD	β-Cyclodextrin
β-CDNS	β-Cyclodextrin-based nanosponge
BGM	Bakuchiol, *Ginkgo biloba* extract, and mannitol
BO	Babchi essential oil
BOMS	Babchi essential oil in microsponge
BONS	Babchi essential oil in nanosponge
CLL	Collagen
DEJ	Dermal-epidermal junction
EC	Ethyl cellulose

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ECM	Extracellular matrix
EMA	European Medicines Agency
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GC-MS	Gas chromatography-mass spectrometry
HDF	Human dermal fibroblast
IL-8	Interleukin-8
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MIF	Macrophage migration inhibitory factor
MMP	Matrix metalloproteinase
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Microsponge
NF-kB	Nuclear transcription factor-Kβ
NO	Nitric oxide
NS	Nanosponge
PGE_2	Prostaglandin E_2
POFR	Phenolic oxygen free radical
PVA	Polyvinyl alcohol
RET	Retinol
ROS	Reactive oxygen species
SC	*Stratum corneum*
TDNA	Percentage of fragmented DNA
TMOM	Tail moment
UV	Ultraviolet

Introduction

Plant-derived products have been widely used for many years, thanks to their cost-effectiveness and easy accessibility. *Psoralea corylifolia* is a widely recognized plant, particularly among Chinese and Indian populations, owing to its natural geographic distribution. Given the decades of ethnobotanical use and its diverse chemical composition, several properties have been ascribed to *P. corylifolia*, encompassing estrogenic, antidepressant, hepatoprotective, immunomodulatory, osteoblastic, neuroprotective, and pesticidal activities (Alam et al. 2018; Chopra et al. 2013; Koul et al. 2019; Li et al. 2016b). It is the source of more than a hundred compounds (Alam et al. 2018; Khushboo et al. 2010; Koul et al. 2019; Li et al. 2016b). Among these compounds, the renowned psoralen stands out, and it has been employed in the treatment of psoriasis since the 1970s (Reid and Griffiths 2020). Bakuchiol (BAK) is also considered one of its main compounds (Chaudhuri and Bojanowski 2014; Chen et al. 2012; Cui et al. 2015; Ferrándiz et al. 1996; Jafernik et al. 2021; Madrid et al. 2015; Majeed et al. 2012; Zhuang et al. 2013). From a chemical standpoint, it has an aromatic ring and a long hydrocarbon chain which negatively influences its water solubility, a relevant aspect for its practical application in carrier systems (Adarsh Krishna et al. 2022). In addition, the BAK molecule has other specific physicochemical properties responsible for its main biological activities.

Over the years, various extraction methods have been described, with one notable approach being an "environmentally friendly" technique utilizing supercritical extraction to acquire BAK (Lewińska et al. 2021). Extracting plant-derived products can be a challenge due to the large number of active compounds present. Frequently, plant extraction and isolation methods yield low quantities of the desired substances. In these cases, chemical synthesis can be used as an alternative. Despite certain challenging steps, several scientists have reported diverse synthetic chemical pathways for BAK (Lystvan et al. 2010).

The organisms constituting the skin's microbiota, known as commensal organisms, play a crucial role in maintaining homeostasis and contribute to reinforcing the skin's immune capacity (Byrd et al. 2018; Parlet et al. 2019). Disturbances in the commensal balance can lead to the overgrowth of fungal and bacterial species. Several in vivo and in vitro studies have confirmed the effectiveness of BAK in addressing these disorders (Cui et al. 2015; Hsu et al. 2009; Lau et al. 2010, 2014; Parlet et al. 2019; Pfaller et al. 2006). *Staphylococcus aureus*, an opportunistic pathogen, is implicated in the majority of acute and chronic bacterial skin infections. It is estimated that approximately 20 to 30% of healthy adults carry *S. aureus* asymptomatically. Moreover, about 76% of skin infections are attributed to *S. aureus* (Parlet et al. 2019). In the face of increasing antibiotic resistance, the antibacterial properties of BAK become especially valuable (Poláková et al. 2015).

Furthermore, the antioxidant and anti-inflammatory properties can be beneficial in slowing down the natural aging process (Bluemke et al. 2022; Heidari et al. 2022; Zafar et al. 2022). Free radicals are naturally produced during biological processes

(Surveswaran et al. 2007). Acute overexposure to solar radiation can lead to sunburn, while chronic exposure may induce skin changes such as wrinkle formation, plaque-like thickening, deep furrowing, and a reduction in skin tone. This condition, commonly referred to as "photoaged skin" or "solar scar", has a particularly negative effect due to the generation of reactive oxygen species (ROS) associated with cellular oxidative damage (Fayad et al. 2017) in DNA, lipids, and proteins, ultimately resulting in a decline in cell viability (Cadet and Wagner 2013; Lau et al. 2014; Slimen et al. 2014). Human exposure to factors such as allergens, microbes, and pollutants contributes to an increased generation of ROS. Maintaining a balance in oxidation-antioxidation processes, along with the presence of systems that monitor the formation of these radicals and facilitate their elimination, is crucial (Bouayed and Bohn 2010; Surveswaran et al. 2007).

In the human body, macrophages play a crucial role in the innate immune response, exhibiting immunomodulatory properties essential for inflammatory response and immune surveillance. Activation of macrophages, typically induced by lipopolysaccharides (LPSs), initiates the activation of transcription factors, such as mitogen-activated protein kinase, nuclear transcription factor-kB (NF-kB), and the secretion of cytokines and proinflammatory mediators, including nitric oxide (NO), prostaglandin E_2 (PGE_2), tumor necrosis factor α, interleukin-1β, and interleukin-6 (Mitra et al. 2022; Qin et al. 2022; Taciak et al. 2018). Blood-circulating monocytes serve as the primary source of skin macrophages, undergoing tissue maturation and differentiation, although they are not found in the epidermis (Kashem et al. 2017; Pae et al. 2001). Macrophages may act as inflammatory mediators in certain inflammatory skin diseases, such as atopic dermatitis (Eichenfield et al. 2014; Weidinger and Novak 2016) and psoriasis (Deng et al. 2016), making them attractive targets for therapeutic interventions aimed at suppressing inappropriate or excessive activation (Chen et al. 2017). In this context, several studies have been conducted to demonstrate the anti-inflammatory capacity associated with BAK.

Among skin cancers, melanoma stands out as one of the most lethal and invasive types. Once it reaches the metastatic stage, its control becomes challenging, often leading to high mortality rates due to a limited response to treatment. The difficulty in obtaining effective anticancer therapy sometimes results in inadequate targeting, resulting in a cytotoxic effect on normal cells. Early diagnosis substantially enhances the prospects of successful treatment (Madrid et al. 2015; Movagharnezhad et al. 2022; Raza et al. 2022). The constant need to search for novel molecules provided the opportunity to discover more about BAK and its potential anticancer properties. As the largest organ in the human body, the skin serves as an excellent avenue for drug delivery. However, molecules with low penetration capacity often require modifications to facilitate this delivery (Lewińska et al. 2021). Particle size reduction is one of the strategies. Micro and nanosponges formulations, as well as nanoemulsions, offer solutions to overcome limiting characteristics such as volatility, hydrophobicity, and viscosity. Additionally, these formulations enhance physical stability and extend the release time of the drug, enabling dose reduction and minimizing side effects (Kumar et al. 2018; Lewińska et al. 2021; Wadhwa et al. 2019).

Regulatory issues play a pivotal role in ensuring the safe use of nanosystems. Regulatory organizations must clarify specific regulations related to the manufacturing process, determination of pharmacodynamic and pharmacokinetic profiles, and evaluation of toxicological profiles. This is crucial to ensure the efficiency and safety of these nanoformulations, thereby securing sustained approval for their market availability (Mascarenhas-Melo et al. 2022).

Physicochemical properties of bakuchiol

BAK's unique chemical composition, structure and molecular arrangement give rise to numerous biological activities (Nazir et al. 2021). Its chemical structure comprises phenolic and terpenoid components, classifying BAK as a meroterpene phenol. The chemical skeleton consists of an aromatic ring with a hydroxyl group and, at the *para* position, an unsaturated long hydrocarbon chain containing three alkenes and one all-carbon (tetra-alkylated) quaternary stereocenter (Adarsh Krishna et al. 2022). BAK possesses an asymmetric stereocenter and its absolute configuration has been shown to exhibit (*S*)-chirality (as illustrated in Fig. 1).

Table 1 summarizes the physicochemical properties of BAK. Due to its long hydrophobic chain, BAK

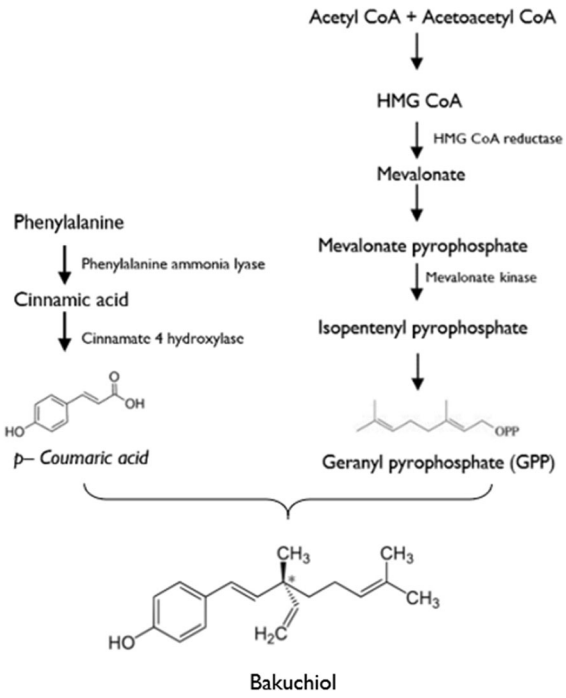


Fig. 1 Biosynthesis of bakuchiol and its molecular structure

has low aqueous solubility and poor bioavailability. Additionally, BAK undergoes a significant degree of first-pass metabolism, due to its easy formation of covalent bonds with endogenous molecules such as glycine and glucuronic acid through the phenolic hydroxyl group (Adarsh Krishna et al. 2022; Li et al. 2021).

Sources of bakuchiol

Natural sources

BAK exhibits structural and chemical diversity. In plants, it is synthesized through a mixed pathway that combines amino acids and isoprene. This synthesis leads to molecular chemical variations in terms of stereocenters and different functional groups contributing to its various biological activities (Adarsh Krishna et al. 2022). Since 1977, efforts have been undertaken to understand the biosynthetic pathways responsible for BAK production. Notable research groups, such as those led by Banerji and Chintalwar, as well as Risinger et al., have contributed significantly to understanding the natural formation of BAK (Banerji and Chintalwar 1983, 1984; Risinger et al. 1978). In a 1978 study, Risinger et al. proposed novel biosynthetic pathways for irregular terpenes, including BAK, suggesting a pivotal role for 2-(1-hydroxy-2-phenylethyl) thiamine as the intermediary in their formation (Risinger et al. 1978). In 1983, Banerji and Chintalwar reported the synthesis pathway of BAK in *P. corylifolia*. They used mevalonic acid and phenylalanine as substrates, demonstrating that BAK has a mixed origin, derived from two isoprenoid units and one phenylpropane (with the loss of the carboxyl carbon) (Banerji and Chintalwar 1983). Subsequently, the same researchers highlighted L-phenylalanine as the preferred precursor over L-tyrosine in BAK biosynthesis, proposing that BAK originates from phenylalanine through *p*-coumaric and cinnamic acids (Banerji and Chintalwar 1984). These findings laid the foundations for recent studies, suggesting that BAK belongs to a distinct group of rare terpenoids, with its aromatic ring derived from the phenylpropane pathway. This phenolic compound has a carbon side chain (monoterpene chain) derived from the mevalonate pathway (Adarsh Krishna et al. 2022; Chaudhuri and Bojanowski 2014). Figure 1 schematically represents one of the described biosynthesis pathways. This mixed pathway starts with phenylalanine and leads to *p*-coumaric acid. Simultaneously, the reaction between acetyl CoA and acetoacetyl CoA produces geranyl pyrophosphate. Finally, the interaction of these two compounds results in the formation of BAK.

While BAK is typically associated with *Psoralea corylifolia,* it has also been extracted from various other species. Examples include *Pimelea drupacea* (Lystvan et al. 2010), *Psoralidium tenuiflorum* (Hsu et al. 2009), *Prosopis glandulosa* (Backhouse et al. 2001; Labbé et al. 1996), *Piper longum* (Ohno et al. 2010), *Aerva sangulnolenta* (Jafernik et al. 2021), *Otholobium pubescens* (Krenisky et al. 1999), *Ulmus davidiana* (Choi et al. 2010; Lee et al. 2021).

The first isolation of BAK occurred in 1973 by Mehta et al. from *P. corylifolia* seeds (Damodaran and Dev 1967). *P. corylifolia* is recognized as the primary source of BAK (Jafernik et al. 2021) and it is also recognized as a synonym of *Cullen corylifolium (*L.*) Medik* (Jafernik et al. 2021; Kim et al. 2018; Liu et al. 2021; Ren et al. 2020; Sharifi-Rad et al. 2020).

Table 2 provides an overview of some extraction methods described for obtaining BAK from natural sources.

Table 1 Physicochemical properties of bakuchiol

Physicochemical properties		References
Molecular formula	$C_{18}H_{24}O$	(Adarsh Krishna et al. 2022; Hsu et al. 2009; NCBI 2022; Takao et al. 2012)
Chemical name	4-[(1*E*,3*S*)-3-ethenyl-3,7-dimethylocta-1,6-dien-1-yl] phenol	(ECHA 2022a; Madrid et al. 2012; NCBI 2022)
CAS	10,309–37-2	(NCBI 2022)
Molecular weight	256.38 g mol^{-1}	(Alalaiwe et al. 2018; Hsu et al. 2009; Husain et al. 2018; Jiangning et al. 2005; NCBI 2022; Takao et al. 2012)
Molecular volume	238.38 cm^3. mol^{-1}	(Alalaiwe et al. 2018)
Organoleptic characteristics[A]	Pale yellow oil Viscous liquid. Brownish-yellow, odor characteristic of aromatic compounds	(Adarsh Krishna et al. 2022; Alalaiwe et al. 2018; Hsu et al. 2009; Jiangning et al. 2005; Madrid et al. 2012; Takao et al. 2012; Xu et al. 2013) (ECHA 2022b)
Boiling point[B]	> 260 °C	(ECHA 2022c)
Flash point[C]	184 °C	(ECHA 2022d)
Partition coefficient[D]	5.09 (octanol–water)	(ECHA 2022e)
Explosiveness	No exothermic decomposition peak was observed up to 430 °C, the test item is considered to be nonexplosive	(ECHA 2022f)
Solubility in 20% PEG400	0.02 mM	(Alalaiwe et al. 2018)
Water solubility[E]	Slightly soluble (0.1–100 mg/L)	(ECHA 2022g)
Density[F]	0.969 g/cm^3	(ECHA 2022h)
Rotatable bond	6	(Adarsh Krishna et al. 2022; Husain et al. 2018; NCBI 2022)
Bioavailability score	0,55	(Husain et al. 2018)
Maximum absorption UV	262 nm	(Hsu et al. 2009; Jiangning et al. 2005)
Optical rotation[G]	+ 37.2°	(Hsu et al. 2009)
iLog P [H]	3.54	(Adarsh Krishna et al. 2022; Husain et al. 2018)
Alog P [I]	5,35	(Alalaiwe et al. 2018)
Log K [J]	0,73	(Alalaiwe et al. 2018)
Molar Refractivity	84.10	(Adarsh Krishna et al. 2022)
Polar Surface Area	20.23 $Å^2$	(Alalaiwe et al. 2018; NCBI 2022)
Surface tension [K]	43.92 mN/m	(ECHA 2022i)
Hydrogen bond accept number	1	(Adarsh Krishna et al. 2022; Alalaiwe et al. 2018; Husain et al. 2018; NCBI 2022)
Hydrogen bond donor number	1	(Adarsh Krishna et al. 2022; Alalaiwe et al. 2018; Husain et al. 2018; NCBI 2022)

[A]Organoleptic characteristics, determined at 20° C. [B]Boiling point, determined at 300 mm Hg atmospheric pressure. [C]Flash point, determined at 760 mm Hg atmospheric pressure. [D]Partition coefficient (log Pow), determined at 20 °C, 6.31 pH, by HPLC. [E]Water solubility, determined at 20 °C, 5 pH. [F]Density, determined at 20 °C. [G]Optical rotation, $[\alpha]^{30}_{D}$ = + 37.2°, exhibited by (+)-BAK. [H]iLog P is the n-octanol/water partition coefficient, accepted as a measure of the lipophilicity of a substance. [I]Alog P is the partition coefficient, determined by molecular modeling. [J]Log K is the logarithm of t_r-t_0, where tr is the retention time of the compost peak and t_0 is the retention time of the solvent peak. [K]Surface tension, determined at 20 °C (1 g/L)

Table 2 Main extraction methods for obtaining BAK from natural sources

Plant material	Extraction method	Extraction conditions	References
Psoralidium tenuiflorum (whole plants)	Ethyl acetate extraction	The sample was extracted with ethyl acetate and dried (rotary evaporation)	(Hsu et al. 2009)
		The ethyl acetate extract was partitioned between hexane and aqueous methanol	
		The methanol fraction was diluted with water and subsequently extracted with dichloromethane	
		Evaporation of solvents yielded two fractions: bioactive dichloromethane and methanol fractions, and an inactive hexane fraction	
		Bioactive fractions were combined, chromatographed, and eluted with increasing quantities of methanol in water	
		Bioactive fractions were combined, chromatographed, and eluted with increasing amounts of ethyl acetate in hexane	
		The most active ethyl acetate fraction was subjected to reverse-phase PTLC with aqueous methanol	
P. corylifolia (fruits)	Ethanol extraction	The sample was extracted with 95% ethanol under reflux and evaporated to dryness	(Lau et al. 2010)
		The ethanolic extract was sequentially partitioned with n-hexane, dichloromethane, ethyl acetate, and n-butanol	
		The hexane fraction was subjected to chromatography and eluted with a mixture of hexane and ethyl acetate (9:1), followed by elution with methanol and water (7:3)	
P. corylifolia (fruits)	Ultrasound-assisted extraction	The sample was mixed with an extraction solvent (methanol and concentrated hydrochloric acid (5:1))	(Chen et al. 2012)
		Ultrasound extraction was carried out at 20 °C for 45 min	
		The mixture was left at room temperature for 30 min	
		The extract was centrifuged at 3000 g for 20 min	
		The supernatant was collected, diluted with the extraction solvent, and stored in a refrigerator at 4 °C	
P. glandulosa (aerial parts)	Dichloromethane extraction	The sample was immersed in dichloromethane for 30 s at room temperature	(Madrid et al. 2012)
		The filtered solution was concentrated under reduced pressure	
		The resin extract was subjected to chromatography and eluted with a mixture of ethyl acetate and hexane	
P. corylifolia (fruits)	n-hexane, ethyl acetate, and methanol extraction	The sample was successively extracted with n-hexane, ethyl acetate, and methanol	(Cui et al. 2015)
		The ethyl acetate extract was subjected to chromatography and purification by HPLC and TLC	
P. corylifolia L (fruits)	Methanol extraction	The sample was extracted with methanol for 3 days	(Chen et al. 2017)
		The extract was concentrated under reduced pressure at 35 °C	
		The residue was partitioned between ethyl acetate and water (1:1)	
		The ethyl acetate-soluble fraction was subjected to several chromatographs, eluted with a mixture of ethyl acetate and hexane and purified by preparative TLC	

Table 2 continued

Plant material	Extraction method	Extraction conditions	References
P. corylifolia (fruits)	Ultrasound-assisted extraction	The sample was extracted with ethanol for 30 min, filtered, and cooled to room temperature The extracted solution was dried, concentrated under reduced pressure at 50 °C, and dissolved in methanol The extract was subjected to HSCCC with a two-phase solvent system of n-hexane–ethyl acetate–methanol-water (5:5.5:6.5:5, v/v/v/v)	(Wu et al. 2020)
P. corylifolia (seeds)	Supercritical Fluid Extraction	The sample was extracted at 280 bar and 40 °C with pure CO_2 at a flow rate of 4 L NPT/min (equivalent to 3.6 g/min) The extraction static/dynamic cycles (10 min in static mode and 20 min in dynamic mode), total extraction duration: 330 min The extract was stored in the dark at -20 °C	(Lewińska et al. 2021)

HPLC High-performance liquid chromatography, HSCCC High-speed countercurrent chromatography, *PTLC* Preparative thin layer chromatography, *TLC* Thin layer chromatography

Regeneration and authenticity of P. corylifolia, and extraction and detection of bakuchiol

Despite being a valuable source of constituents such as BAK, *P. corylifolia* faces the threat of endangerment. Given this problem, is crucial to understand how we can produce and conserve this species, preventing overexploitation and mitigating the risk of extinction (Jani et al. 2015; Koul et al. 2019). In addition, factors including geographical location, climatic variations, and environmental conditions introduce variability in the chemical composition, potentially influencing its pharmacological effects (Wu et al. 2020). Ensuring the production of high-quality products is essential to guaranteeing customer safety and the desired therapeutic effect (Heinrich 2015; WHO 2022). The use of standardized techniques to verify the authenticity and prevent counterfeiting becomes necessary, especially with species like *Abutilon theophrasti* Medic. and *Crotalaria pallida*. Despite their morphological similarities, these species exhibit distinct characteristics in terms of chemical composition (Wu et al. 2020).

Lewińska et al. reported a new "green" method with various advantages, including low extraction temperature and short operating times. This approach effectively reduces thermal degradation and oxygen decomposition of bioactive compounds. Additionally, pure CO_2 serves as an appealing solvent due to its odorless, inert, non-toxic, and non-inflammable properties. It is cost-effective and facilitates the solubility of hydrophobic compounds. The technique employs the static-dynamic method, involving alternating cycles of static extraction (10 to 15 min) and dynamic extraction (15 to 50 min). This method enables the extraction of a high BAK content with a lower percentage of psoralens and isopsoralen, which typically require higher pressure and temperature values. The highest yield, about 8.58%, was obtained with 10/20 intervals at 280 bar for 330 min. Since BAK extraction occurs at the initial stages of the process, a high process yield is not required to obtain a BAK-rich extract. Therefore, the key to obtaining high BAK contents lies in optimizing the extraction process conditions (Lewińska et al. 2021). Several separation techniques have already been documented and, depending on the chosen method, different compounds can be extracted and isolated. Chen et al. further explored this issue, suggesting that high-performance liquid chromatography coupled with electrochemical detection is the most suitable technique for the separation, identification, and quantification of BAK due to its high sensitivity (Chen et al. 2012).

Table 3 summarizes the key findings from studies regarding the previously mentioned issues.

Table 3 Summary of research studies on in vitro regeneration and authenticity of *P.corylifolia*, and extraction and detection of bakuchiol

	Background	Hypothesis	Desired result	Results	References
P. corylifolia regeneration in vitro	This medicinal herb is difficult to propagate due to low seed germination, and elevated seedling mortality	Supplement the medium with growth regulators: 6-Benzylaminopurine and Kinetin to regenerate *P. corylifolia* in vitro from root fragments	Obtain in vitro high shoot bud/explant and elongated shoot from root fragments	Maximal response (65.57%) was observed when the medium was supplemented with 2.22 µM 6-Benzylaminopurine and 6.98 µM Kinetin. They exert a positive synergistic effect	(Jani et al. 2015; Koul et al. 2019)
Prove the authenticity of *P. corylifolia*	Therapeutic activities and active ingredient concentration are directly related to plant quality. Low-quality products compromise customer safety and the intended therapeutic effect	The analytical method High-Speed Countercurrent Chromatography might serve as a fingerprint	Use a standard technique to verify the authenticity and prevent counterfeiting	Chromatograms present six peaks that amount to certain marker compounds for inferring plant quality	(Heinrich 2015; WHO 2022; Wu et al. 2020)
"Green"Extraction of BAK	An extensive range of extraction techniques with different methods, solvents, and experimental conditions has been described to obtain BAK from *P. corylifolia* seeds	Extract BAK from *P. corylifolia* seeds through a Supercritical Fluid Extraction with pure carbon dioxide	Found a sustainable alternative to conventional solvent-based extraction methods	SCFE performed at 280 bar and 40 °C with a CO_2 flow rate equivalent to 3.6 g/min, allows to obtain nearly 80% of BAK	(Lewińska et al. 2021)
Achieve a final product of excellence	To achieve a final product of excellence, it is necessary to establish quality standards, such as qualitative and quantitative composition, that must be compliant with an acceptable range of values	The most common technique is High-Performance Liquid Chromatography, which can be coupled to varying detectors	Choose the detector that is most suitable for the separation, identification, and quantification of BAK	HPLC coupled with electrochemical detection seems to be the most appropriate technique for the separation, identification, and quantification of BAK due to its high sensitivity	(Chen et al. 2012)

BAK Bakuchiol, *HPLC* High-performance liquid chromatography; *SCFE* Supercritical fluid extraction

Chemical synthesis

BAK can be isolated from various plant species, but it is also obtained through chemical synthesis. Since its discovery in 1966, several approaches to the chemical synthesis of BAK have been explored. However, these pathways are complex and often result in racemic BAK (±) instead of the optically active (+)-isomer found in nature (Lystvan et al. 2010). Total synthesis involves achieving crucial stereochemistry and an all-

Table 4 Chronologically-ordered synthetic pathways of bakuchiol

Year	Final product	Reactional first steps and brief general notes	References
1967	*Rac*-bakuchiol methyl ether	Geraniol interacts with ethyl vinyl ether First chemical synthesis Three-step synthesis	(Adarsh Krishna et al. 2022; Damodaran and Dev 1967)
1967	*Rac*-bakuchiol	Geraniol reacts with p-methoxyacetophenone diethyl acetal First total synthesis of *rac-bakuchiol* Prepared in situ Claisen rearrangement: a key step to obtain the bakuchiol skeleton	(Adarsh Krishna et al. 2022; Araki and Bustugan 1991; Carnduff and Miller 1967)
1990	(+)-bakuchiol	(*S*)–O-benzylglycidol reacts with methyl First enantioselective synthesis of (+)-bakuchiol Twelve-steps synthesis	(Adarsh Krishna et al. 2022; Takano et al. 1990)
1991	*Rac*-bakuchiol	Geranylindium sesquibromide reacts with 2-(4-methoxyphenyl) acetaldehyde Synthesis via a geranylindium reagent. Three-step synthesis	(Adarsh Krishna et al. 2022; Araki and Bustugan 1991)
1999	(+)-bakuchiol	Sequential alkylation of cyclohexanone with Lithium diisopropylamide-allyl bromide and Lithium diisopropylamide - methyl iodide Synthesis via stereoselective alkylation using silyl group to obtain the chiral quaternary carbon center. Sixteen steps with an overall yield of 5%	(Adarsh Krishna et al. 2022; Sakakiyama et al. 1999)
2008	(+)-bakuchiol	Chiral Michael's acceptor reacts with Copper-Lithium reagent Synthesis via stereoselective alkylation using silyl group. 1,4 addition using vinylcopper (I) reagents. Ten-step synthesis	(Adarsh Krishna et al. 2022; Esumi et al. 2008)
2008	*Rac*-bakuchiol	Intermediate prepared with vinyl magnesium bromide and Grignard reagent Synthesis via 1,4 addition of citral, with vinylmagnesium bromide under Cu (I) catalyst. Four-step synthesis	(Adarsh Krishna et al. 2022; Chen and Li 2008)
2008	(*S*)-bakuchiol (*R*)-bakuchiol	Geraniol undergoes Sharpless epoxidation Method of obtaining chiral center. Synthesis of (*S*)-enantiomer in ten steps. Synthesis of (*R*)-enantiomer in nine steps	(Adarsh Krishna et al. 2022; Du et al. 2008)
2009	(+)-bakuchiol	Conversion of (−)-citronellol into citronellol-based chiral ∂-sulfone Synthesis via intramolecular diazosulfonate obtaining C–H bond	(Adarsh Krishna et al. 2022; Bequette et al. 2009)
2010	(+)-bakuchiol	Geraniol phosphonation Synthesis via Ni Catalyzed NCH–Cu enantioselective allylic substitution reaction	(Adarsh Krishna et al. 2022; Gao et al. 2010)
2012	(+)-bakuchiol	Geraniol reacts with N-propioloyl camphorsultam (Michael addition reaction) Synthesis via sulfur-based chiral auxiliaries-mediated Claisen rearrangement	(Adarsh Krishna et al. 2022; Takao et al. 2012)
2013	(*S*)-bakuchiol	Geranic acid reacts with triethylamine and pivaloyl chloride Synthesis via asymmetric 1,4-addition	(Adarsh Krishna et al. 2022; Esumi et al. 2013)
2013	(*S*)-bakuchiol	Stereo-selective unconjugated alkylation of an α, β-unsaturated imide Asymmetric synthesis routes. An approach using Evans' auxiliary	(Adarsh Krishna et al. 2022; Xu et al. 2013)
2016	(*S*)-bakuchiol	Geranial diazo is added to 4-methoxy phenyl boronic acid solution Synthesis of bakuchiol precursor in one single operation, using an interactive coupling method	(Adarsh Krishna et al. 2022; Battilocchio et al. 2016)

Table 4 continued

Year	Final product	Reactional first steps and brief general notes	References
2016	(*S*)-bakuchiol	Chiral oxazoline sulfonamide ligand and a chromium salt provide allylation products Asymmetric allylation to obtaining quaternary center Method through chromium-catalyst	(Adarsh Krishna et al. 2022; Xiong and Zhang 2016)
2017	(*S*)-bakuchiol methyl ether	Rhodium-catalyzed hydroboration of pinacolborane with allylic phosphonates Strategy via enantioselective rhodium-catalyzed hydroboration	(Adarsh Krishna et al. 2022; Chakrabarty and Takacs 2017)
2020	*Rac*-bakuchiol	Tertiary allylic carbonate reacts with sulfinate salt Used a regioselective molybdenum-catalyzed and allylic substitution	(Adarsh Krishna et al. 2022; Salman et al. 2020)

carbon quaternary (tetra-alkylated) stereocenter. Moreover, obtaining alkenyl groups between carbons 17 and 18, a sterically hindered position, entails a specific challenge (Adarsh Krishna et al. 2022; Choudhury et al. 2017; Harding 2006; Hawner and Alexakis 2010; Quasdorf and Overman 2014).

Table 4 presents the synthetic pathways reported by various authors over time in chronological order. This table offers a succinct overview of the different approaches, accompanied by brief explanations of the respective processes.

Skin bioactivities of bakuchiol

Antifungal activity

BAK exhibits remarkable antifungal properties, evidenced by lower minimum inhibitory concentration values compared to traditional antifungals. Studies evaluating the antifungal efficacy of BAK against species such as *Candida guilliermondii* and *Trichophyton mentagrophytes* have demonstrated highly promising results, surpassing the effectiveness of conventional antifungals. *C. guilliermondii* is commonly associated with superficial skin infections (Pfaller et al. 2006), while *T. mentagrophytes* is a dermatophyte linked to athlete's foot, also known as tinea pedis (Bell-Syer et al. 2012; Ilkit and Durdu 2015). Additional parameters indicating the effectiveness of BAK include an increased permeability of the fungal membrane, as demonstrated by Lau et al. leading to fungal death due to an increase in ROS and not as a consequence of DNA fragmentation (Lau et al. 2014). The primary outcomes of various studies on the antifungal properties of BAK are summarized in Table 5.

Antibacterial activity

BAK also demonstrates significant antibacterial activity, as pointed out by Yin et al., who considered BAK as a "well-known natural antimicrobial agent". In their study, BAK was used as a positive control, with minimum inhibitory concentration values of 0.018 and 0.037 mM observed for *Staphylococcus epidermidis* and *S. aureus*, respectively (Yin et al. 2004). *S. epidermidis* is a common bacteria found on healthy human skin (Brown and Horswill 2020) and can be the causative agent of certain opportunistic skin infections (Natsis and Cohen 2018; Nguyen et al. 2017). Methicillin-resistant *S. aureus* (MRSA) has also been associated with skin infections (Lee et al. 2018). Trompezinski et al. evaluated the efficacy of the biological complex BAK, *Ginkgo biloba* extract, and mannitol (BGM), and compared it with benzoyl peroxide and zinc gluconate. Benzoyl peroxide, a topical agent commonly used as a first-line treatment for acne, generates free radicals to damage the bacterial cell walls of *Cutibacterium acnes* (also known as *Propionibacterium acnes*) (Eichenfield et al. 2021). Zinc gluconate has a bacteriostatic effect against *C. acnes* and is also employed in acne management (Yee et al. 2020). Table 6 summarizes the main results of some studies, emphasizing the lower inhibitory concentration values exhibited by

Table 5 Main results of studies conducted to evaluate the antifungal activity of bakuchiol

Bakuchiol source	Study models	Positive Controls	Results	Conclusions	References
P. glandulosa (aerial parts)	In vitro Microdilution method for yeast	Fluconazole, ketoconazole, and itraconazole	BAK showed ↓ MIC_{80} MIC_{80}: BAK = 0.125 µg/mL Fluconazole = 0.5 µg/mL Ketoconazole = 0.5 µg/mL Itraconazole = 4.0 µg/mL	BAK exhibited better activity against *C. guilliermondii* than the other antifungals tested	(Madrid et al. 2012)
P. corylifolia (dried ripe fruit)	In vitro Broth dilution method	Fluconazole	BAK showed ↓ MIC MIC: BAK = 3.83 µM Fluconazole = 52.20 µM	BAK exhibited better activity against *T. mentagrophytes* than the other antifungal tested	(Lau et al. 2010)
P. corylifolia (dried ripe fruit)	In vitro Broth dilution method	Terbinafine and nystatin	BAK showed ↑ fungal membrane permeability and ↑ROS levels Fungal membrane permeability: BAK > Terbinafine > Nystatin ROS levels in fungal cells: Nystatin > BAK > Terbinafine	BAK does not induce DNA fragmentation in *T. mentagrophytes* BAK increases fungal membrane permeability dose-dependently and generates ROS	(Lau et al. 2014)
P. corylifolia (dried ripe fruit)	In vivo Hartley guinea pigs	Lamisil® cream (Terbinafine)	BAK (aqueous cream) eradicates fungal hyphae and eliminates the fungal burden in guinea pigs´ paws but was not as effective as Lamisil®	The discrepancy between the activity of BAK and Lamisil® was attributed to the absence of transdermal enhancers or formulation issues that compromise appropriate drug delivery	(Lau et al. 2014)

BAK Bakuchiol, *MIC* Minimum inhibitory concentration, *ROS* Reactive oxygen species

Table 6 Main results of studies conducted to evaluate the antibacterial activity of bakuchiol

Bakuchiol source	Study models	Positive Controls	Results	Conclusions	References
P. corylifolia (fruits)	In vitro Liquid dilution method	NA	BAK showed ↓ MIC against MRSA (strains) compared to flavones, isoflavones, meroterpenes, and coumarins	BAK exhibited activity against both MRSA strains (OM481 and OM584) This antibacterial activity depends on the presence of phenolic hydroxyl groups and lipophilicity provided by the benzene ring	(Cui et al. 2015)
P. tenuiflorum (Ethyl acetate extract)	In vitro Agar well diffusion method	NA	IC_{12}: BAK = 123 ± 11 µg/mL	BAK displayed cytotoxicity against *S. epidermidis*	(Hsu et al. 2009)

BAK Bakuchiol, ***BGM*** Bakuchiol, *Ginkgo biloba* extract, and mannitol, ***IC*** Inhibitory concentration; *MIC* Minimum inhibitory concentration, ***MRSA*** Methicillin-Resistant *S. aureus*; *NA* Not applicable

BAK compared to other compounds, underscoring its antibacterial potential.

Antioxidant activity

The antioxidant properties of BAK result from the presence of hydrogen in the terpenoid chain, located conveniently adjacent to the trisubstituted alkene group and readily available for abstraction. Additionally, the antioxidant activity is influenced by the enthalpy of dissociation of the phenolic bond (Adhikari et al. 2003). Another critical factor that increases antioxidant activity is the presence of hydroxyl groups in the aromatic ring, along with the reinforcement of electron-donating groups, especially in the *ortho*- and *para*-positions. Conversely, electron withdrawal diminishes these antioxidant properties. Additionally, the stereo-hindering effect of hydroxyl groups, especially in the *ortho*-position, modulates antioxidant activity.

Jiangning et al. characterized BAK as an unhindered phenol, emphasizing the absence of substituted groups in the *ortho*-positions of the hydroxyl group. A pivotal double bond links the phenol of the phenolic hydroxyl group in the *para*-position. This structural configuration enables the extension of BAK's phenolic oxygen free radical (POFR) conjugation system after the donation of a hydrogen atom to active free radicals. As a result, the resonance structure stabilizes POFR, reinforcing its antioxidant efficacy (Jiangning et al. 2005). Studies have been conducted to elucidate the antioxidant activity of BAK.

C. acnes absorbs ultraviolet (UV) and visible radiation, resulting in the photo-oxidation of squalene, a sebaceous lipid prone to oxidation due to its chemical structure with six double bonds. Squalene peroxides play a role in various skin conditions, including acne (Cibrian et al. 2020). The skin naturally produces vitamin E, a lipophilic antioxidant present in normal human sebum, to prevent squalene oxidation. Vitamin E production is directly correlated to the amount of squalene. In individuals with acne, low levels of vitamin E contribute to increased levels of oxidized squalene (Thiele et al. 1999; Trompezinski et al. 2016).

Trompezinski et al. also evaluated the efficacy of the BGM complex in treating acne vulgaris, while Bluemke et al. explored the multidimensional and holistic impact of BAK on cellular aging. BAK demonstrates the ability to protect biological components, specifically proteins and lipids, from oxidative damage. Furthermore, BAK exhibits a superior ability to eliminate free radicals compared to retinol (RET). ROS trigger an inflammatory cascade that results in reduced cell viability in both dermal and epidermal cells, leading to extracellular matrix (ECM) damage—a recognized cornerstone of skin aging. These findings support the antiaging effect of BAK through its strong antioxidant activity (Bluemke et al. 2022).

Table 7 brings together the results from various research groups regarding the antioxidant properties of BAK.

Anti-inflammatory activity

Pro-inflammatory cytokines, such as interferon-γ and LPS, have the ability to stimulate the expression of inducible nitric oxide synthase (iNOS). The iNOS gene comprises a promoter and a repeated initial sequence that facilitates the binding of transcription factors, including NF-kB, associated with stimuli triggering iNOS expression. After synthesis, iNOS generates high and sustained levels of NO, a crucial inflammatory mediator for host defense. The quantification of NO synthesis can be obtained by measuring the accumulation of nitrite in the culture medium. However, its sustained production has been implicated in the pathogenesis of inflammatory diseases. The anti-inflammatory response is related to the suppression of NO activity (Pae et al. 2001).

Both PGE_2 and macrophage migration inhibitory factor (MIF) are pro-inflammatory cytokines. High levels of these cytokines are observed in aging skin due to chronic exposure to UVA and UVB irradiation. Despite this similarity, they follow distinct signaling pathways. PGE_2, the main prostaglandin produced in human skin, has the capacity to reduce collagen (CLL) synthesis and increase the expression of matrix metalloproteinase (MMP) in fibroblasts (Bluemke et al. 2022). On the other hand, MIF is expressed in the skin, particularly in fibroblasts and keratinocytes. Acting as a potent macrophage activator, MIF positively regulates UVA-induced MMP-1 in fibroblasts (Shimizu 2005). BAK effectively reduces the levels of these cytokines, which demonstrates its anti-inflammatory activity and underlines its antiaging effects (Bluemke et al. 2022).

Table 7 Main results of studies conducted to evaluate the antioxidant activity of bakuchiol

Bakuchiol source	Study models	Positive Controls	Results	Conclusions	References
BGM complex (cream)	In vitro Squalene oxidation	Vitamin E	Prevention of squalene oxidation: At 3.9 mM At 19 mM BAK–30.0% BAK–36.9% Vit E–15.2% Vit E–40.3%	The protective index of BAK squalene was 2x↑ that of vitamin E	(Trompezinski et al. 2016)
Sytenol® A (from Sytheon Ltd)	In vitro DPPH reduction and electron spin resonance	Retinol	Antioxidant power: BAK—12,125 antioxidative unit RET—848 antioxidative unit	BAK exhibits ↑ antioxidant capacity and power than RET	(Bluemke et al. 2022)

BAK Bakuchiol, *BGM* Bakuchiol, *Ginkgo biloba* extract, and mannitol; *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *RET* Retinol, *Vit E* Vitamin E

Chen et al. conducted a screening for potential natural anti-inflammatory agents, using RAW 264.7 cells previously exposed to LPS to induce NO production (Chen et al. 2017). Other studies, particularly those by Pae et al. explored the inhibition of iNOS gene expression (Pae et al. 2001). Bluemke et al. focused their research on assessing the anti-inflammatory capacity of BAK, examining its effect on reducing two pro-inflammatory cytokines, PGE_2 and MIF (Bluemke et al. 2022).

Table 8 summarizes the main results of these studies focusing on the anti-inflammatory activities of BAK.

Antiaging activity

Several factors contribute to skin aging, including exposure to UV radiation throughout life. The degradation of ECM is one of the main signs of aging. This damage causes the degeneration of dermal connective tissue and is marked by the degradation of CLL fibers, elastic fibers, and hyaluronic acid (Fayad et al. 2017).

BAK has the potential to prevent skin aging through different pathways, delaying the appearance of signs of aging. While comparable to RET, BAK's efficacy surpasses that of this well-known compound. In addition, it should be noted that the antioxidant and anti-inflammatory activities of BAK produced promising results, demonstrating an impact on the aging process.

BAK's anti-aging effects can be attributed to its "retinol-like" activity, since BAK acts as a functional analog of RET. However, its anti-aging effect may also be associated with other mechanisms termed "non-retinol-like", which will be described below.

Non-retinol-like activity

Bacqueville et al. studied the in vitro benefits of BAK in preventing skin photoaging. The actin network serves as an aging marker that facilitates morphological analysis. After UVA irradiation, actin staining showed that human dermal fibroblasts (HDFs) lose their star-shaped pattern and acquire a fusiform pattern. Incubation with 0.5 µg/mL BAK effectively prevented the morphological changes in fibroblasts, with results comparable to those of the non-irradiated/non-treated control. Furthermore, after UVA irradiation, there was an increase in the expression of interleukin-8 (IL-8) and P16 protein, both indicative of

Table 8 Main results of studies conducted to evaluate the anti-inflammatory activity of bakuchiol

Bakuchiol source	Study models	Positive Controls	Results	Conclusions	References
P. corylifolia (dried fruits)	In vitro Murine macrophage cell line RAW264.7	Quercetin	BAK showed ↓ IC_{50} IC_{50}: BAK = 21.57 μM Quercetin = 33.08 μM	BAK inhibits NO generation LPS-induced, without cytotoxicity (cell viability > 93%)	(Chen et al. 2017)
P. corylifolia (seeds)	In vitro Murine macrophage cell line RAW264.7	Pyrrolidine dithiocarbamate	Inhibition of NF-kB activation (measured through nitrite accumulation) Pyrrolidine – potent inhibition BAK – similar inhibition, slightly higher Transcriptional regulation (measured through expression of iNOS mRNA) INF-γ/LPS—considerably increase BAK—decrease its expression	BAK acts at the transcriptional level to regulate iNOS gene expression, through NF-kB binding dose-dependently inhibition	(Pae et al. 2001)
P. corylifolia (seeds)	In vitro Human dermal fibroblasts	Diclofenac	PGE_2 levels: BAK considerably reduced the PGE_2 level and at10 μM had a similar reduction as a positive control MIF protein levels: BAK considerably reduced MIF levels	BAK proved to considerably reduce the expression of two pro-inflammatory cytokines (PGE_2 and MIF)	(Bluemke et al. 2022)

BAK Bakuchiol, *IC* Inhibitory concentration, *INF-γ* Interferon gamma, *iNOS* Inducible nitric oxide synthase, *LPS* Lipopolysaccharides, *MIF* Macrophage migration inhibitory factor, *NF-kB* Nuclear factor kappa B, *NO* Nitric oxide; *PGE_2* Prostaglandin E2

skin aging. Incubation with BAK led to a reduction in the expression of IL-8, associated with inflammation, and P16, linked to cellular senescence (Fig. 2A) (Bacqueville et al. 2020).

Subsequently, the authors investigated the benefits of *Vanilla tahitensis* extract (VTE) and BAK, exploring the potential of the compounds alone and in combination to prevent skin photoaging. In in vitro studies, the combined compounds showed a significant synergistic effect, resulting in a remarkable reduction of 95.1% in IL-8 expression. While the individual reductions were 88.3% for BAK and 83.8% for VTE, the combined impact was notably higher. There was also a reduction in P16 levels of around 95.2%, with individual reductions of 44.4% and 29.2% for BAK and VTE, respectively (Fig. 2B) (Bacqueville et al. 2020). It is noteworthy that, despite the synergistic effect, both results showed the superior efficacy of BAK when used alone.

To better understand the advantages of this combination, a dermo-cosmetic serum was formulated (1.5% BAK + 1% VTE), and an ex vivo study was conducted using a model of photodamaged human skin induced by chronic UVA irradiation. Glycosaminoglycan (GAG) was used as an ECM marker to assess dermal density. GAG is located near the dermo-epidermal junctions (DEJ) and the underlying papillary dermis. Chronic exposure to UVA radiation

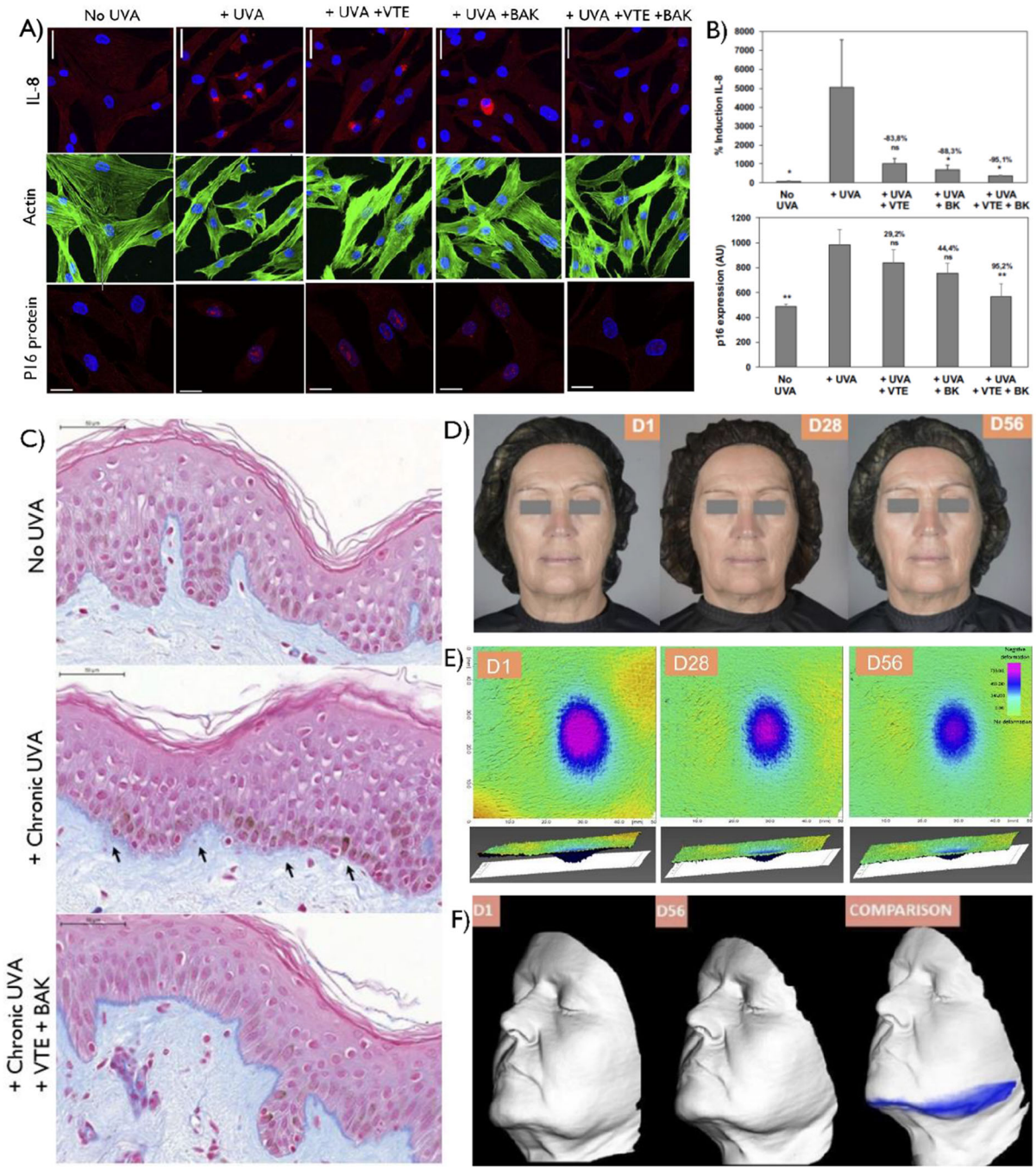


Fig. 2 Antiaging effect of BAK. **A** Immunofluorescence staining of actin network, interleukin-8, and p16 protein as markers of morphology, inflammation, and senescence, respectively. Performed in human dermal fibroblasts. Analyzed by laser scanning confocal microscopy; **B** Quantitative analyses of IL-8 and p16 immunolabelling; **C** Evaluation of dermal density in an ex vivo human skin aging assay. Analyzed by photon microscopy. Arrows indicate GAG (intense blue network) loss at the dermo-epidermal junction; **D** Full-face macrophotographs show improvement of radiance after 28 days (+ 26%) and 56 days (+ 44%); **E** Skin firmness improvement, analyzed by Dynaskin®. Cross-section showing the depth of skin deformation reduced after 28 and 56 days. In the image below, from day 1 to day 56, skin deformation depth 56 days (30.4%), and skin deformation volume 56 days (36.7%); **F** Facescan®, ptosis volume decreased 56 days (22.8%). Defined face contour, showing a remodeling effect of the product. Adapted from (Bacqueville et al. 2020)

induces photoaging stress, resulting in a decline in ECM production, particularly in GAGs, and disrupts the network, leading to less intense and more diffuse staining (Fig. 2C). The loss of GAGs is correlated with changes in the CLL and elastic fibers in the papillary dermis. The application of this serum demonstrated the ability to restore GAG content and network organization, thereby improving dermal density. The results were comparable to the non-irradiated/ non-treated control, indicating that the serum exhibited a re-densifying effect and protected the skin from UVA-induced changes in GAGs (Bacqueville et al. 2020; Lee et al. 2016; Naylor et al. 2011).

The researchers concluded the serum evaluation with a clinical trial involving 43 healthy women, where skin radiance through photographs, firmness using DynaSKIN®, and skin remodeling with FaceScan® were assessed. The clinical trial revealed significant outcomes in skin radiance, with an overall improvement of approximately 20% observed in 80% of individuals after 56 days (Fig. 2D). The dermatological assessment revealed an improvement in skin firmness in 95% of individuals, evidenced by a decrease in skin deformation of 17% and 16% in depth and volume, respectively (Fig. 2E). Furthermore, after 56 days, 63% of individuals reported a significant remodeling effect, characterized by a more defined facial contour line (Fig. 2F). The results for tolerance and overall safety rated the serum as "very good" (Bacqueville et al. 2020).

Additionally, the main results of the studies by Bacqueville et al. are found in Table 9, as well as the results of the in vivo study by Bluemke et al., where the efficacy of 0.5% BAK cream was compared with its vehicle involving 34 healthy individuals (Bluemke et al. 2022).

Retinol-like activity Retinoids play a crucial role in maintaining skin health, and any deficiency or excess of these compounds can disrupt the natural balance of the skin, leading to disturbances in homeostasis and impairment of the skin's barrier function (Fisher and Voorhees 1996). Within this group of natural compounds, retinol (vitamin A alcohol), retinal (vitamin A aldehyde) and retinoic acid (vitamin A acid) are the most important elements (Bailly et al. 1998; Chaudhuri and Bojanowski 2014). As active derivatives of vitamin A, they play key roles in various stages of the cell life cycle, including differentiation, proliferation, and apoptosis (Bastien and Rochette-Egly 2004).

Due to the importance of RET in controlling and regulating homeostasis and natural cellular processes, along with the reported side effects associated with its use, a current fundamental premise is to identify an alternative molecule that can exert similar effects with minimal adverse effects. Despite lacking structural similarities with retinoids, BAK has the ability to perform similar functions, earning its classification as a functional analog (Chaudhuri and Bojanowski 2014).

Chaudhuri et al. conducted an investigation into the relationship between BAK and retinoids, revealing their structural dissimilarity, as illustrated in Fig. 3. In an effort to identify potential RET-like compounds, the study involved a comparison of gene expression profiles with the known RET profile. The results of this genome-wide analysis are represented by a volcano plot for both BAK and RET (Fig. 4A), where significant changes in DNA microarray data are highlighted. The positively regulated genes are situated on the right, while negatively regulated genes are on the left. The general similarity in the shapes of the volcano diagrams for both compounds served as evidence of the functional analogy between these molecules. This was further confirmed by the similar modulation of genes involved in retinoid-binding and metabolism (Chaudhuri and Bojanowski 2014).

RET positively regulates nuclear retinoid receptors, responsible for translating retinoid signals (Bastien and Rochette-Egly 2004), whereas BAK does not influence their modulation. This suggests potential advantages in terms of adverse effects (Napoli 2017). BAK significantly up-regulates lecithin-retinol acyltransferase, responsible for the esterification of RET with a long chain of fatty acids, essential for the absorption and storage of RET. Furthermore, both BAK and RET up-regulated the retinoic acid receptor responsive gene, typically down-regulated in acne, psoriasis, rosacea, and multiple human cancers, making BAK an attractive candidate for the treatment of these health conditions. These results not only indicate that BAK increases the endogenous bioavailability of RET, but also highlight its role as a functional analog of it (Chaudhuri and Bojanowski 2014).

Moreover, BAK has been shown to up-regulate genes encoding ECM components in DEJ, specifically those associated with CLL fibrils and elastin

Table 9 Main results of studies conducted to evaluate the anti-aging activity of bakuchiol, including non-retinol-*like* and retinol-*like* activity

	Bakuchiol source	Study models	Results	References
Non-retinol-*like* activity	*P. corylifolia* (seeds)	In vitro Human dermal fibroblasts	BAK reduced the expression of IL-8, p16 protein and prevented fibroblast morphological changes	(Bacqueville et al. 2020)
		Ex vivo Human skin explants	BAK exhibits a re-densifying effect and protects skin from GAG alterations UVA-induced in human skin photodamaged model	
		In vivo Human volunteers	BAK exhibits a remodeling effect, reduced depth and volume, and improved skin firmness and radiance	
	P. corylifolia (seeds)	In vivo Human volunteers	BAK was well tolerated and improved the perceived appearance of the skin regarding radiance, freshness, and signs of skin aging	(Bluemke et al. 2022)
Retinol-*like* activity	*P. corylifolia* (seeds)	In vitro DNA microarrays	Up and downregulation of genes (ECM and DEJ). Similar RET gene modulation profile	(Chaudhuri and Bojanowski 2014)
		Ex vivo Human EpiDermFT skin substitute	BAK increased collagen synthesis and metabolic activation in mature fibroblasts and AQP3 expression	
		In vivo Human volunteers	BAK improved photodamage signs (skin elasticity, tone, brightening, dryness, wrinkles)	
	P. corylifolia (seeds)	In vivo Human volunteers	BAK exhibit good efficacy (clarity, radiance, overall global photoaging, overall skin appearance, tactile softness, and visual smoothness) and tolerability (redness, peeling, burning, itching, dryness, tightness, erythema, flaking, irritation, roughness, stinging) in sensitive skin, with an excellent tolerability profile	(Draelos et al. 2020)

AQP3 Aquaporin-3, *BAK* Bakuchiol, *DEJ* Dermo-epidermal junctions, *ECM* Extracellular matrix, *GAG* Glycosaminoglycans, *IL-8* Interleukin 8, *RET* Retinol, *UVA* Ultraviolet A

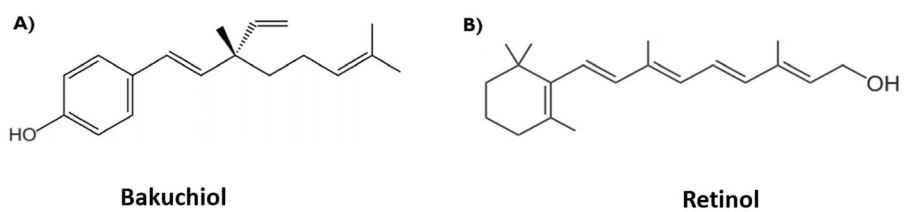
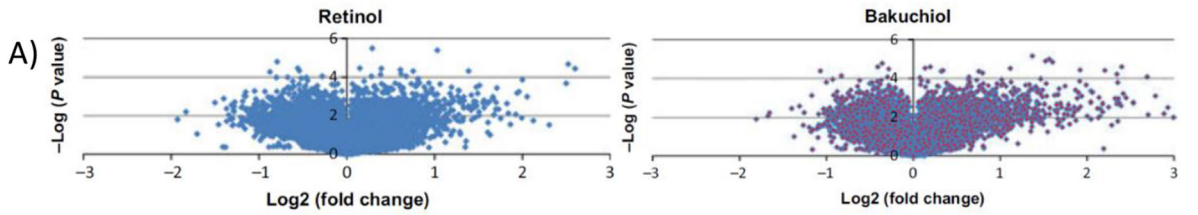
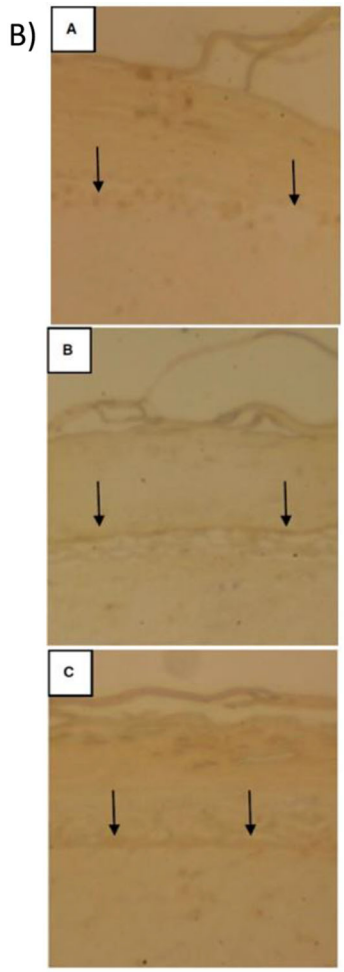


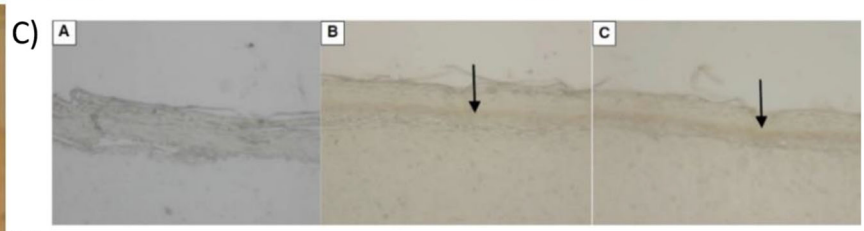
Fig. 3 **A** Structure of Bakuchiol; **B** Structure of Retinol

microfibrils. The degradation of these components is directly linked to the appearance of wrinkles and fine lines, as they play a significant role in the tensile strength and elasticity of the skin's support structure (Tsamis et al. 2013).

BAK also demonstrated a notable up-regulation of the genes encoding fibronectin-like, hyaluronan synthase 3, and aquaporin 3 (AQP3), surpassing the effects observed with RET. Fibronectin contributes to the stability of the matrix and is indispensable for

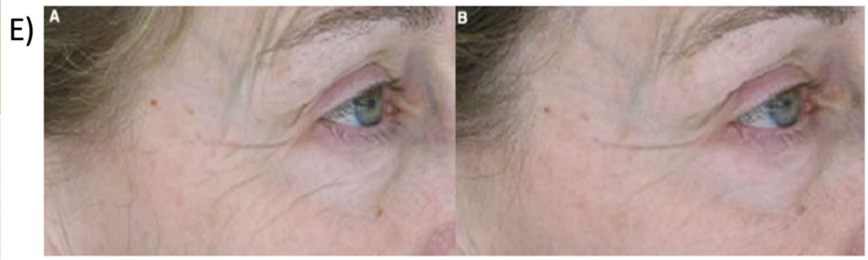






D)

Parameters	4 Weeks E	4 Weeks I	8 Weeks E	8 Weeks I	12 Weeks E	12 Weeks I
Roughness & dryness	65	35	81	40	90	48
Fine lines/wrinkles	5	19	16	25	29	23
Skin tone	14	12	29	19	39	29
Skin elasticity/firmness	13	14	20	23	39	25
Radiance	24	11	40	17	52	30
Skin brightening	13	10	35	14	46	29
Eye area appearance	8	22	24	24	46	35



F)

Parameters	4 Weeks	8 Weeks	12 Weeks
Wrinkle depth	−7%	−13%	−20%
Skin roughness	−2%	−10%	−21%

Fig. 4 **A** Volcanic plot of DNA microarray data for RET and BAK; **B** RET **b** and BAK **c** effect on collagen IV expression in human EpidermFT (full thickness), **a** is the control. Arrows indicate DEJ, where collagen IV is localized. Darker bands in **b** and **c** confirm collagen expression; **C** RET **b** and BAK **c** effect on AQP-3 expression in human EpidermFT (full thickness), **a** is the control. Arrows indicate AQP-3 staining in the basal layer, where is mainly localized; **D** Subjective evaluation by experts **E** and individuals **I** (% improvement vs. baseline); **E** Right view day zero VS 12-week treatment; **F** Results of silicone replica analysis using profilometry: % reduction vs. baseline. Adapted from (Chaudhuri and Bojanowski 2014)

maintaining the shape of cells, while hyaluronan preserves tissue hydration. AQP3, a channel protein present in the epidermis, is involved in water/glycerol transport, contributing to skin hydration, barrier recovery, and elasticity (Chaudhuri and Bojanowski 2014). BAK also promoted the positive regulation of certain genes in DEJ, which provide cohesion between the epidermis and dermis, namely CLL α-6 (IV), involved in cellular processes such as migration, proliferation, and adhesion, and CLL α-2 (XVII),

which strengthens the bond between the two skin layers (Chaudhuri and Bojanowski 2014). On the other hand, BAK also positively regulated components of hemidesmosomes, such as plectin I and integrins, which play roles in cellular functions, such as cytoskeleton organization. Additionally, BAK influenced laminin, a key protein in the *lamina densa*, associated with cell survival and phenotypes (Chaudhuri and Bojanowski 2014).

It is crucial to highlight that RET is renowned for its ability to inhibit natural aging signals, such as morphological flattening and thinning of the skin, which result from the physiological weakening of the ECM and DEJ. BAK emerges as a promising candidate in the realm of anti-aging, showcasing a gene upregulation profile that, in most instances, surpasses that of RET (Chaudhuri and Bojanowski 2014). In photodamaged and aged skin, the synthesis of CLL decreases as a result of the quantitative and qualitative reduction of fibroblasts. BAK stimulated the expression of CLL in a mature fibroblast model by 147%, 150%, and 119% for type I, II, and IV, respectively, whereas the RET results were 119%, 148%, and 100%, respectively, under identical conditions (Chaudhuri and Bojanowski 2014).

BAK and RET were incubated at 10 μg/mL with a 3D model of a skin tissue substitute (EpiDerm FT) to assess whether the stimulation of type IV CLL corresponded to robust CLL expression. The result revealed a strong signal near the DEJ, visible when using an anti-type IV CLL antibody (Fig. 4B), suggest that CLL synthesis results from selective metabolic activation in fibroblasts, as BAK does not promote cell proliferation (Chaudhuri and Bojanowski 2014). Epidermal water homeostasis is crucial for the hydration of the *stratum corneum* (SC), which is essential for maintaining protective function, mechanical properties, and a healthy appearance of the skin. Dehydration of the SC is common in photoaged skin and diseases like psoriasis, eczema, and atopic dermatitis. EpiDermFT, when incubated with BAK, exhibited an increase in the expression of the AQP3 gene in DNA microarrays, correlating with an elevation in the protein's quantity (Fig. 4C) (Chaudhuri and Bojanowski 2014).

It is also important to note that when RET undergoes oxidation in the skin, it produces retinoic acid, which mimics its effects but is noticeably less irritating. Even at the usual concentration of RET, less than or equal to 0.1%, some irritation can occur. In this context, BAK exhibits better acceptability and tolerability on the skin. Chaudhuri et al. concluded their research with a clinical study involving 16 subjects who applied the 0.5% BAK formulation twice a day for 12 weeks. Experts and individuals evaluated parameters such as skin elasticity, tone, brightness, dryness, wrinkles, radiance, and eye area appearance, using a semi-quantitative scale, where 0 corresponds to none and 4 to severe. Experts gave higher ratings to radiance, roughness, and the percentage of improvement in dryness, while individuals gave higher ratings to the eye area appearance, fine lines, and wrinkles. A pronounced improvement in most parameters was observed at week 8 compared to week 4, suggesting cumulative beneficial effects of BAK over time (Fig. 4D) (Chaudhuri and Bojanowski 2014). The study also evaluated profilometry, analyzing wrinkle depth and skin roughness using a silicone replica. The reduction in wrinkle depth was 7%, 13%, and 20% after 4, 8, and 12 weeks, respectively. Similarly, the reduction in skin roughness was 2%, 10%, and 21% after 4, 8, and 12 weeks, respectively (Figs. 4E and 4F). All these significant improvements in photodamage signs observed 12 weeks after treatment with BAK corroborate the in vitro results, supporting its therapeutic potential as a valid alternative to RET (Chaudhuri and Bojanowski 2014).

Topical retinoids have been used for many years, often associated with frequently reported adverse effects, including irritation, burning sensation at application sites, erythema, pruritus, and flaking (Mukherjee et al. 2006). Individuals with sensitive skin may experience even more pronounced effects. Addressing these concerns, Draelos et al. (Draelos et al. 2020) conducted a clinical evaluation of BAK as a nature-based antiaging product. The study included 60 women with three dermatologic conditions: 20 with atopic dermatitis/eczema, characterized by a breakdown of the barrier, 20 with rosacea, associated with vascular hyperreactivity, and another 20 with cosmetic intolerance syndrome, defined as individuals with a history of harmful sensory stimuli in response to topical applications. BAK demonstrated retinoid-like effects due to RET-like genetic modulation, but with a significantly improved tolerance profile compared to retinoids and without the need for dose scaling. In this study, a cleanser and antiaging moisturizer based on

BAK (1% w/w) were used and the main results are also presented in Table 9 (Draelos et al. 2020).

Depigmenting

A study conducted by Kang et al. evaluated the effect of the UP256 cream, composed of 77.02% BAK, on reducing hyperpigmentation. The effect of UP256 in inhibiting melanin synthesis was assessed in vitro using normal human epidermal melanocytes and compared with phenylthiourea, a melanogenesis inhibitor. UP256 at 5 μM demonstrated a similar inhibition of melanin production as phenylthiourea at 10 μM. Additionally, tyrosinase activity was detected in situ by staining with L-3,4-dihydroxyphenylalanine. An increase in UP256 concentration led to a reduction in the stained area. Western blot analysis revealed a decrease in the expression of melanogenic enzymes and the pull-down assay showed a pronounced inhibition of the activation of the GTP-binding protein, which is involved in the formation of melanocyte dendrites. The authors also analyzed the effect of UP256 in vivo, using an embryonic zebrafish model, and ex vivo, in a 3D human skin model. The results showed a clear inhibition of melanogenesis by UP256 in both models (Kang et al. 2020).

Lyons et al. conducted an in vivo assessment of the anti-hyperpigmentation effect of BAK. The study involved 20 individuals with acne-induced post-inflammatory hyperpigmentation, characterized by hypermelanosis that occurs after the resolution of skin conditions such as acne, eczema, and psoriasis, following infections, contact dermatitis, allergic reactions, medication use, inflammatory diseases, and burns. The results showed significant improvements in acne-induced post-inflammatory hyperpigmentation lesions after treatment with BAK (Lyons et al. 2020). Table 10 presents the main findings from these studies focusing on the depigmenting activity of BAK.

Anticancer

Madrid et al. investigated the in vitro anticancer potential of BAK against human melanoma cell lines (A2058) and fibroblasts. BAK exhibited significant inhibition of A2058 cell viability without affecting the cell viability of fibroblasts. The authors concluded that cytotoxicity was not attributed to cell membrane rupture. As there was no evidence of cell damage, it was suggested that the inhibition was related to apoptosis (Madrid et al. 2015). Human cancer cells often resist programmed cell death (apoptosis), a natural defense mechanism against tumoral development (Hanahan and Weinberg 2011). This resistance allows tumor progression, making cancer cells resistant to human defense mechanisms and therapeutic interventions (Madrid et al. 2015). Detailed analysis of DNA fragmentation patterns enables the differentiation of necrotic from apoptotic cells. The percentage of fragmented DNA (TDNA) and tail moment (TMOM) are parameters used to determine DNA damage. The results showed an increase in TDNA and TMOM, implying that BAK induces cell death through apoptosis (Madrid et al. 2015). The increase in caspase-3 enzyme activity, correlated with BAK concentration, reinforced the idea of apoptosis induction. Active caspases inhibit cell growth and are involved in the cleavage of proteins crucial for apoptosis. Additionally, western blot analysis assessed the expression of the p53 family, functioning as a stress sensor in the cell and promoting the activation of pro-apoptotic genes and specific proteins, including the pro-apoptotic protein Bax and the anti-apoptotic Bcl-2 family. The Bax/Bcl-2 ratio, reflecting the propensity for apoptosis, demonstrated an increase in Bax protein values and a decrease in Bcl-2 values. In vitro studies showed a down-regulation of Bcl-2 expression and an up-regulation of p53 and Bax in A2058 cells when incubated with BAK. Finally, a concentration-dependent rise in ROS levels (initiating the apoptosis cascade) was observed following the incubation of A2058 cells with BAK (Madrid et al. 2015). Therefore, the results indicate that BAK is effective in vitro in reducing the viability of A2058 cancer cells and exhibits good biocompatibility due to its selective toxicity against cancer cells.

Skin delivery systems for the encapsulation of bakuchiol

The skin, recognized as the largest organ in the human body, serves as an appealing avenue for topical delivery, offering advantages over oral, parenteral, and intravenous administration, particularly in terms of user comfort (minimal pain and invasiveness). Despite their therapeutic or cosmetic applications, active molecules face some challenges, particularly

Table 10 Main results of studies conducted to evaluate the depigmenting activity of bakuchiol

Bakuchiol source	Study models	Conclusions	References
P. corylifolia (seeds)	In vitro Normal human epidermal melanocytes	UP256 cream (77.02% BAK) inhibited melanin production through inhibition of tyrosinase activity, reduction of the expression of TRP 1 and 2, MITF, and α-PAK, inhibition of Rac1 and Cdc42 activation	(Kang et al. 2020)
P. corylifolia (seeds)	In vivo Zebrafish model Ex vivo 3D human skin model	BAK inhibited melanogenesis and exhibited a better depigmenting effect on the skin than the zebrafish model	
P. corylifolia (seeds)	In vitro Normal human epidermal melanocytes	BAK improved acne-induced post-inflammatory hyperpigmentation lesions	(Lyons et al. 2020)

BAK Bakuchiol, *MITF* Microphthalmia-associated transcription factor, *TRP* Tyrosinase-related protein

their limited ability to penetrate through the SC, thus compromising their permeation (Lewińska et al. 2021). Several strategies have been explored to overcome this problem.

BAK demonstrates potential as a therapeutic substance for skin application, with its use currently restricted to cosmetics and personal care products, as defined by the European Chemicals (ECHA 2022j).

Formulations incorporating BAK as a cosmetic ingredient are already available on the market, specifically designed to reduce fine lines and wrinkles, improve skin elasticity, increase CLL synthesis, and even out skin tone, among other benefits. Table 11 provides examples, summarizing their main characteristics and claims. Unfortunately, the specific delivery systems for these formulations are not publicly known. This section will look at three nanosystems for topical delivery, offering detailed descriptions that will contribute to future studies on skin BAK delivery.

Bakuchiol-loaded microsponges

Wadakwa et al. explored a new approach for delivering the essential oil of *P. corylifolia* (Babchi) (BO) to the skin by encapsulating it in microsponges (MS). Babchi essential oil, widely employed in traditional medicine, poses challenges due to its volatile nature, low solubility, and stability (Wadhwa et al. 2019). The production of Babchi oil microsponges (BOMS), as described by Pawar et al., followed the quasi-emulsion solvent evaporation method, utilizing ethyl cellulose (EC) as a hydrophobic, non-swellable cellulose derivative for structural integrity. Polyvinyl alcohol (PVA) served as an emulsifier and stabilizer, while dichloromethane acted as a solvent (Pawar et al. 2015). Gas chromatography-mass spectrometry (GC–MS) confirmed BAK as the main constituent of BO. Essential oils compositions can vary slightly based on factors such as the growing environment, harvest and collection time, and extraction technique, among other considerations (Wadhwa et al. 2019).

The MS structures are predominantly spherical and highly porous, with multiple null spaces for BO encapsulation (Wadhwa et al. 2019). After confirming the viability and stability of the BO in the microstructures, the researchers analyzed the in vitro drug release profile. In general, the cumulative percentages of drug release are inversely proportional to the concentrations of the polymer and emulsifier. Increased concentrations of EC and PVA led to a decrease in the extent of drug release. For instance, higher EC content reduces the surface accumulation of the drug (drug accumulated in the polymeric matrix), delaying the release rate. A low amount of EC results in small MS with a high surface area, increasing the release rate (Wadhwa et al. 2019).

Despite the excellent properties of some essential oils, certain ones have shown skin toxicity and irritation. The results of the BOMS compatibility studies conducted by Wadakwa et al. are shown in

Table 11 Commercialized products containing bakuchiol and their claims

Concerns	Product categories	Activity claims of bakuchiol	Commercial Brands	References
Fine lines & wrinkles	Serum Cream Gel-Cream	RET-like effect by its action on CLL I synthesis stimulation	Laboratoires Lierac Paris (Cica-filler)	(Lierac 2022a; 2022b; 2022c)
Imperfections	Gel	↓ sebum secretion (acts on shine)	Laboratoires Lierac Paris (Sébologie)	(Lierac 2022d)
Imperfections/ acne-prone skin	Cream	Part of SeboRestore technology; Helps restore natural sebum quality	Bioderma (Sébium global)	(Bioderma 2022; Poláková et al. 2015; Trompezinski et al. 2016)
Fine lines & wrinkles	Serum	Restoring skin elasticity and firmness (stimulation on CLLs and elastin fibers synthesis); ↓ fine lines appearance and wrinkles	ISDIN (Melatonik)	(Goldberg et al. 2019, 2020; ISDIN 2022; Narda et al. 2018, 2020)
Fine lines & wrinkles/ Maturing skin	Cream	Moisturizer; ↑ collagen production; Improves skin texture and tone	Skintensive (Bakuchiol + Retinol)	(Skintensive 2022)
Fine lines & wrinkles	Cream	Improves skin firmness and elasticity; ↓ fine lines appearance and wrinkles; Improve skin tone	TheInkeyList (Bakuchiol Moisturizer)	(Theinkeylist 2022)
Fine lines & wrinkles	Cream Serum	↓ fine lines appearance and wrinkles; Improves skin elasticity; Improve even skin tone and smooth texture	Olehenriksen (Transform Plus)	(Olehenriksen 2022a; 2022b)
	Eye Gel-Cream	Fades the look of lines around the eyes; ↓ fine lines appearance and wrinkles; Improves even skin tone and smooth texture; Improves skin firmness, elasticity and the look of dark circles	Olehenriksen (Transform)	(Olehenriksen 2022c)
Fine lines & wrinkles	Serum	↓ CLL degradation and ↑ its synthesis; Improves skin firmness; ↓ expression lines and wrinkles; Regulates sebum and evens out skin tone; ↓ hyperpigmentation and imperfections, correct the dark spots	*Be* beauty (Bakuchiol)	(Olehenriksen 2022d)

Table 11 continued

Concerns	Product categories	Activity claims of bakuchiol	Commercial Brands	References
Skin tone & elasticity	Serum	↑ skin elasticity and even out skin tone	Rituals (Natural Booster)	(Rituals 2022)
Fine lines & wrinkles	Night cream Day cream	Defines the contours; Regenerates the skin; ↓ deep wrinkles; Activate cellular CLL; Redensifies and strengthens the skin's support fibers	NIVEA (Cellular expert lift)	(Nivea 2022a; 2022b)
Anti-Aging/ Brown spots	Serum	Stimulates the effect of retinol; ↓ discoloration; Fades brown spots and evens out a patchy skin tone	Paula's Choice (Clinical)	(Paula's 2022a)
Anti-Aging	Cream	Improves skin tone and texture; Fades brown spots; ↓ fine lines appearance and wrinkles	Paula's Choice (Clinical)	(Paula's 2022b)
Anti-Aging	Serum	RET-like effect; ↓ fine lines appearance and wrinkles; ↓ discoloration; Improves skin firmness	Biossance (Squalane + phyto-retinol)	(Biossance 2022)
Anti-Aging	Serum Booster Eye Cream Oil	Improves skin hydration, firmness and elasticity; ↓ fine lines appearance and wrinkles; Improve skin tone	Allies of Skin (Bakuchiol)	(Allies 2022a, 2022b, 2022c, 2022d, 2022e)

CLL Collagen, *RET* Retinol

Table 12. In general, the developed microformulation demonstrated greater safety on keratinocytes compared to free BO, showcasing compatibility with skin cells (Wadhwa et al. 2019). Previous studies have highlighted the antibacterial effect of BAK against a variety of bacteria, particularly *S. aureus* and *S. epidermidis* (Chopra et al. 2013), MRSA (Cui et al. 2015), *Pseudomonas aeruginosa*, and *Escherichia coli* (Li et al. 2021). In vitro, BOMS displayed robust antimicrobial activity, comparable to streptomycin (standard drug), and notably superior when compared to free BO (Wadhwa et al. 2019).

Furthermore, photodegradation studies suggest that BOMS are more photostable than free BO, which is attributed to the encapsulation of BO in the MS system forming a physical barrier. This protects the BO from UVA-induced photolysis, improving its photostability. These findings hold significance for pharmaceutical applications, since microencapsulation can safeguard bioactive substances from degradation by UVA radiation. Additionally, stability studies indicate no color change in the MS over 3 months, implying no significant difference in their content (Wadhwa et al. 2019).

Thus, the MS system proves to be an effective and stable approach for the dermal delivery of BO. Beyond its demonstrated antibacterial properties and minimal propensity for antibiotic resistance, MS could offer a promising strategy for treating dermatological infectious disorders. The use of the MS system allows the main limiting characteristics of BO to be overcome, such as its volatile nature, hydrophobicity, high

Table 12 Summary of main properties and characteristics of skin delivery systems for Bakuchiol

Formulation	Pharmaceutical form	Characterization	Preparation method	Composition	Bakuchiol content	EE (%)	LE (%)
P. corylifolia (Babchi) essential oil, encapsulated in microsponges (BOMS)	Microsponges	Spherical uniform shape with a highly porous microstructure	Quasi-emulsion solvent evaporation method	-Babchi essential oil -Ethyl cellulose (polymer) -Polyvinyl alcohol (emulsifier and stabilizer) -Dichloromethane (solvent)	65,37%	55.28 to 87.70	NA
Babchi essential oil encapsulated in β-cyclodextrin-based nanosponges (BONS)	Nanosponges	Fluffy powder with a highly porous structure losing its crystallinity	Blank β-cyclodextrin nanosponges: Melt method Essential oil loading: Freeze-drying method	-Babchi essential oil -Diphenyl carbonate (crosslinker)	65,37%	50.43 to 93.05	14.23 to 21.47
Bakuchiol loaded in nanoemulsions	Nanoemulsions	Oil-in-water; Spherical nanostructures with roughly uniform sizes, non-aggregated and good droplet distribution	Spontaneous and sustainable self-assembly process between Bakuchiol and surfaction and coco-betaine	-Bakuchiol -Surfactin and coco-betaine (stabilizers) -Oil -Water	80%	NA	NA

Formulation	Particle size	Zeta potential (mV)	Poly Dispersity Index	Release profile (in vitro)	Cytotoxicity	Antibacterial activity Inhibition zone (mm)	Reference
P. corylifolia (Babchi) essential oil, encapsulated in microsponges (BOMS)	20.44 to 41.75 µm	NA	NA	58.35 to 86.21% (after 8 h)	→ In immortalized human keratinocytes Free Babchi oil at 320 µg/mL caused 51.05% inhibition BOMS at 320 µg/mL caused 26.34% inhibition BOMS did not have a significant cellular cytotoxic effect	Free Babchi oil: *P. aeruginosa* 11.67 *E. coli* 11.33 *S. aureus* 12.67 BOMS: *P. aeruginosa* 16.77 *E. coli* 15.33 *S. aureus* 16.67	(Wadhwa et al. 2019)

Table 12 continued

Formulation	Particle size	Zeta potential (mV)	Poly Dispersity Index	Release profile (in vitro)	Cytotoxicity	Antibacterial activity Inhibition zone (mm)	Reference
Babchi essential oil encapsulated in β-cyclodextrin-based nanosponges (BONS)	234 to 484 nm	-22.0 to -15.5 ↑values: (↑ repulsive forces) greater stability with less aggregation trend	0.188 to 0.509 ↓values: homogeneous and stable nanocolloidal suspensions	NA	→ In immortalized human keratinocytes Free Babchi oil the IC_{50} value was 172.3 µg/mL BONS the IC_{50} value was 191.4 µg/mL BONS formulation is safer than free Babchi oil for human skin cells	Free Babchi oil: *P. aeruginosa* 12.33 *E. coli* 12.00 *S. aureus* 12.33 BONS: *P. aeruginosa* 16.00 *E. coli* 17.00 *S. aureus* 16.00	(Kumar et al. 2018)
Bakuchiol loaded in nanoemulsions	200 to 243 nm	-73 to -66	0.182 to 0.276	NA	→ In human dermal fibroblasts and in immortalized human keratinocytes Bakuchiol [0.02 and 0.5] mg/mL showed low cytotoxicity, even at 0.5 mg/mL, the higher concentration Cell viability was reduced by about 60% after 24 h and 55% after 48 h Between 0.02 to 0.2 mg/mL there was a beneficial effect, accompanied by excellent cell survival	NA	(Lewińska et al. 2021)

BOMS Babchi oil microsponges, *BONS* Babchi oil nanosponges, *EE* Encapsulation efficiency, *IC* Inhibitory concentration, *LE* Loading efficiency, *NA* Not available

viscosity, and susceptibility to degradation during storage due to low stability to air, light, and high temperatures. These challenges hinder its utilization in dermopharmaceutical applications. Apart from enhancing stability, the MS system mitigates dermal toxicity, a crucial aspect of therapy adherence. It has shown no cytotoxicity, which is in line with its compatibility with skin cells. The dermatological potential of BOMS can be further optimized by incorporating them into creams, gels, lotions, or other suitable dermal carriers, reinforcing the skin benefits of BO and contributing even more to avoiding skin toxicity problems resulting from direct contact with BO. This delivery system allows for an extended drug release time, thus reducing dosage and potential side effects. Simultaneously, it improves cost-effectiveness and payload (Wadhwa et al. 2019).

Bakuchiol-loaded nanosponges

Following the studies carried out by Wadhwa et al. on BOMS, Kumar and Rao, expanded the research and developed a delivery system for this essential oil, transitioning from the microscale to the nanoscale (Kumar et al. 2018; Wadhwa et al. 2019). Kumar et al. focused on the encapsulation of BO in nanosponges (NS) (BONS) based on β-cyclodextrin (β-CD) (β-CDNSs) (Kumar et al. 2018). The nanocavities within the solid mesh network of β-CD allow for the entrapment of complex chemical substances. NSs are generally highly efficient and significantly enhance stability (Pawar et al. 2019).

Once again, GC–MS confirmed that BAK was the predominant component. The NSs were synthesized using the β-cyclodextrin melt method, which was cross-linked with diphenyl carbonate. Subsequently, the NSs were loaded with essential oil using the freeze-drying method. Thermogravimetry showed that the degradation of cross-linked structures exhibited good thermal stability, and X-ray powder diffraction revealed a loss of crystallinity after freeze-drying, resulting in a fluffy powder characterized by a highly porous structure (Kumar et al. 2018). The main results of the cytotoxicity studies of β-CDNSs are presented in Table 12, indicating that BONSs are generally safer on keratinocytes than free BO, demonstrating compatibility with skin cells (Kumar et al. 2018).

Furthermore, photodegradation studies suggest that BONS are more photostable than free BO due to the encapsulation of BO in the NS system. This protective mechanism delays the photolysis process of the BO induced by UVA radiation, enhancing its photostability. These findings offer additional value for dermopharmaceutical applications, as nanoencapsulation can protect bioactive substances from degradation caused by UVA radiation (Kumar et al. 2018).

In the context of antimicrobial efficacy against various bacteria, including *E. coli, P. aeruginosa,* and *S. aureus*, the performance of BO stands out. BONS also exhibited greater antimicrobial activity in vitro compared to free BO. This significant improvement is attributed to the increased water solubility of BO after its encapsulation in CDNSs, overcoming the limitations of free BO such as volatility and insolubility (Kumar et al. 2018).

The advantages of this formulation are similar to those of MS, serving as a skin delivery system designed to overcome the challenges associated with essential oils. The prolonged drug release time enables a reduction in dosage and drug consumption, thus minimizing the side effects resulting from targeted drug release in the skin. This system reinforces the BO´s dermatological potential while avoiding skin irritation and toxicity. In fact, scale reduction can be advantageous for improving parameters such as solubility and permeability, depending on the intended purpose, due to the substantial increase in the surface area of the particles (Kumar et al. 2018).

Bakuchiol-loaded nanoemulsions

Lewinska et al. recently conducted a comprehensive investigation into "environmentally-friendly" nanoemulsions as a potential strategy to improve the transdermal delivery of BAK. The "green" nanosystem consists of an oil-in-water nanoemulsion with two hybrid-surface active agents (stabilizers), surfactin and coco-betaine (1:4). The inclusion of these ionic surfactants allows for the development of stable formulations (Lewińska et al. 2021).

The prepared nanoemulsions showed high kinetic stability, featuring spherical nanostructures with well-distributed and nearly uniform sizes. In addition, there was no aggregation of nanodroplets, avoiding

processes such as flocculation or coalescence. The formulation containing BAK was subsequently subjected to ex vivo permeation studies, in vitro cytotoxicity, and in vivo contact studies (Lewińska et al. 2021).

The ex vivo study was carried out on Franz cells (full-thickness pig skin). Analysis of the fluid in the acceptor chamber did not detect the presence of surfactants. Subsequently, microscopic analysis revealed that the BAK formulation penetrated the epidermal barrier. The carrier remained intact and provided stable transport (Lewińska et al. 2021). The in vitro study showed that the encapsulated BAK formulation exhibited low cytotoxicity on immortalized human keratinocytes and HDF. BAK proved to be biocompatible in both cell lines (Lewińska et al. 2021). In the in vivo study, which involved male and female volunteers aged between 30 and 50 years, the efficacy of the nanoemulsion (BAK at 0.05 mg/mL) on capillaries, skin discoloration, and wrinkles was evaluated. Younger individuals typically show milder signs of skin deterioration, with softer changes expected. Skin changes in individuals over 40 are usually visible to the naked eye. From the age of 50, some changes become permanent. The results showed that the BAK formulation improved skin condition by reducing the depth of wrinkles and blood vessels in subjects of all ages. Regarding discoloration, there was a significant reduction in subjects aged 30 and 50, which was more evident in those aged 50 (Lewińska et al. 2021). This promising nanoemulsion can increase the solubility and effectiveness of hydrophobic compounds due to its surface-to-volume. In addition to its excellent physical stability, the presence of biosurfactants protects the system from degradation during production and storage. Finally, nanoemulsions are potential systems for the effective delivery of active ingredients, such as BAK, to deeper layers of the skin, as they can penetrate the epidermis, while maintaining its integrity (Lewińska et al. 2021).

Table 12 brings together some of the most important aspects of formulations for delivering BAK to the skin, such as pharmaceutical form, characterization, preparation method, composition, content of BAK, encapsulation efficiency, loading capacity, particle size, polydispersity index, drug release profile, as well as cytotoxicity and antibacterial activity.

Safety of bakuchiol for skin: regulatory and toxicological concerns

Regulatory organizations, including the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), are responsible for developing guidelines for toxicity assessment. In the European Union, the EMA supervises the use of medicines, monitoring their risk–benefit ratio and safety. In addition, all nanocarriers require a full risk assessment evaluation and prior authorization before use (Mascarenhas-Melo et al. 2022). In Europe, EU Directive 2001/83/EC regulates medical products, and EU Directive 93/42/EEC regulates medical devices. One of the critical points is deciding whether nanotechnology-based formulations are medical products or devices (Santos et al. 2020). The toxicity assessment provides efficacy and safety results that determine whether regulatory approval is accepted or denied. The International Organization for Standardization, associated with the Organization for Economic Cooperation and Development, has developed industry standards for assessing the toxicity of nanoformulations. However, these regulations were specifically designed for industrial applications (Cláudia Paiva-Santos et al. 2022; Li et al. 2016a, 2019; Santos et al. 2020). The FDA‘s draft guidance on industrial nanomaterials is not clear on toxicity assessment. It only refers to the importance of establishing a safety profile (Santos et al. 2020).

Concerning BAK, the European Chemicals Agency has compiled a variety of information. The results for the classification of physical hazards were conclusive, but insufficient to classify almost all parameters as explosive or self-reactive substances, except in the case of desensitized explosives, where the reason for non-classification was a lack of data. Concerning health risks, skin irritation/corrosion was assessed in 111 individuals using a patch test, revealing no irritation, and similar results were observed for skin sensitization. The results were conclusive, but insufficient to classify skin sensitization and irritation/corrosion. Additionally, acute dermal toxicity was not classified due to a lack of data (ECHA 2022k). Although it is suggested that BAK may offer advantages over retinoids, potentially preventing side effects such as redness, peeling, itching, erythema, irritation, roughness, and stinging, the reported cases nevertheless indicated adverse reactions. A 33-year-old woman

with no previous atopic history experienced itchy and erythematous plaques, mainly located on the neck, perioral area, and eyelids. Patch tests were performed on the products used, and Noreva Exfoliac Global 6 cream showed a positive result. All ingredients were subjected to patch tests, read on the 3rd and 7th days. BAK was evaluated at 0.1%, corresponding to its concentration in the cream. The result was positive (+++) on the 3rd day. The patient was counseled to avoid products containing BAK (Malinauskiene et al. 2019). In another case, a 23-year-old woman with a history of seasonal rhinoconjunctivitis frequently experienced facial eczema. The woman reported recurrent flares of edematous and erythematous itchy lesions. This coincided with the application of DermAbsolu Soin, an anti-aging eye cream. Patch tests were conducted and read on the 2nd and 4th days, with negative results for all patches. The eye cream was investigated using the repeated open application test, revealing positive results from day one, showing a follicular inflammatory pattern. BAK was evaluated at 1%, corresponding to its concentration in the cream. In the end, only the BAK test was positive (++). The patient was counseled to avoid products containing this compound (Raison-Peyron and Dereure 2020).

The environmental risks classified BAK as "very toxic to aquatic life", in the short-term (category acute 1) and "with long-lasting effects", in the long-term (category chronic 1). BAK labeling includes an environment hazard pictogram (GHS09) (ECHA 2022l, 2022m). Short-term toxicity (ECHA 2022n) was assessed in aquatic invertebrates (*Daphnia magna*), and the results were read after 48 h. The effect concentration (EC_{50}) was around 0.2 mg/L. The toxicity results for algae and cyanobacteria (*Raphidocelis subcapitata*) were read after 72 h, and EC_{50}/NOEC was > 2.108 mg/L (ECHA 2022o). The complete environmental impact of BAK remains unknown, lacking data on aspects such as photodegradation or bioaccumulation (ECHA 2022p). Biodegradation studies in water were conducted using a sample from the Daman Ganga river as an inoculum. The percentage of degradation was estimated by monitoring the consumption of dissolved oxygen over 28 days (the initial concentration was 7.98 mg/L). The results were read on days 7, 14, 21, and 28, and the values obtained were 34.72, 66.89, 77.62, and 87.66%, respectively. BAK was considered not easily biodegradable. Potassium hydrogen phthalate was the reference substance (toxicity control) and showed similar degradation values. The study concluded that BAK had no adverse effects on the inoculum (ECHA 2022p).

Toxicity is closely related to structural and physicochemical properties, including size, shape, tendency to agglomerate, and surface charge (Paiva-Santos et al. 2021). The nanometric dimension entails potential risks. On the one hand, it increases the possibility of achieving systemic circulation and, on the other, it increases the contact surface area. Therefore, more interactions with biological systems are expected, making them more reactive and with a greater potential for toxicity, especially in vivo (Cláudia Paiva-Santos et al. 2022). In addition, cytotoxicity depends on the exposure time and the concentration of the nanosystem, and potential contamination during the manufacturing process should be taken into account (Paiva-Santos et al. 2021). However, more attention should be given to the toxic characteristics of the surface material, since it can influence the surrounding environment (Mascarenhas-Melo et al. 2022). Depending on their ratio, the presence of surfactants may also induce some adverse effects, including irritation, erythema, or toxicity (Santos et al. 2020). Some strategies, including the coating of nanosystems, have been designed to mitigate these toxic effects (Prajitha et al. 2019). However, more studies are required to establish the safety and toxicological profiles of BAK skin delivery systems, both in the short and long-term (Cláudia Paiva-Santos et al. 2022).

Despite all the advantages and great potential of nanoformulations for therapeutic and cosmetic applications, their practical usefulness depends entirely on their favorable safety profile. It is, therefore, necessary to establish a regulatory framework for nanotechnology-based formulations, encompassing specific manufacturing regulations, determining pharmacodynamic and pharmacokinetic profiles, and evaluating toxicological profiles. Only in this way can the efficacy and safety of these nanoformulations be guaranteed, allowing sustained approval for their placement on the market (Paiva-Santos et al. 2021).

It is also important to remember that, although it is intended for topical application, it is essential to know about BAK metabolic pathways. The human liver microsomes, which include several isoenzymes such as CYP2C9, CYP2C19, and CYP3A4, are responsible

for BAK metabolism. This issue is highly relevant due to potential interactions, which can result in adverse reactions or a lack of therapeutic efficacy. It is important to consider the possibility of coadministration of molecules capable of activating or inhibiting any of these isoforms, such as glycyrrhetinic acid, the active metabolite of licorice, which can increase the toxicity of BAK by inhibiting its detoxification enzymes. The inhibition of cytochrome P450 isoenzymes ultimately delays metabolic detoxification, prolonging the time that the drug remains in the body. This can be dangerous due to the increased potential for bioaccumulation and cytotoxicity (Li et al. 2016a). It should also be noted that salt processing reduces the toxicity of *P. corylifolia* extract on the renal and cardiovascular systems. This is attributed to a reduction in volatile compounds, one of which is BAK, resulting from the heating process (Li et al. 2019).

Hsu et al., in their study on the antibacterial effect of BAK, found a curious aspect about its long-term storage. After 8 months at room temperature, BAK degraded into 4-hydroxybenzaldehyde, and showed no antibacterial effect against *S. epidermidis* (Hsu et al. 2009). This compound formed is inactive. These results demonstrate the need for further studies to predict these changes and assess their toxic potential, as well as the possible occurrence of unexpected biological effects.

Conclusions and future perspectives

This review article addresses the main physicochemical properties, natural sources, synthesis routes, biological effects, skin delivery carriers, and toxicity of BAK. It also highlights the existence of a promising "green" method for its isolation, which already has a very successful yield. As far as chemical methods are concerned, none of them stand out for their better performance, so existing methods could be improved, especially from a sustainable perspective. Furthermore, the main skin activities of BAK found in the literature were thoroughly described and discussed, and the results were promising, especially as an anti-aging agent and as a bio-retinol-like agent. BAK appears to be an alternative to RET without its associated adverse effects, even in individuals with sensitive skin. Moreover, it has shown potential antioxidant, anti-inflammatory, and depigmenting effects. Evidence about its anticancer potential is still scarce, but seems promising. BAK also showed antibacterial and antifungal activity against *C. guilliermondii*, MRSA, *S. epidermidis* and *C. acnes*, among others. It can be considered a valuable therapeutic weapon, given the emerging antibacterial resistance. However, its mechanisms of action require further clarification. Concerning BAK skin delivery technology, the delivery systems described are promising in overcoming limiting characteristics such as volatility, hydrophobicity, viscosity and susceptibility to degradation. Future research should expand on the results already found, as well as try to find other delivery systems for BAK, since the alternatives found in the literature are still scarce. In addition, a challenge for the years ahead will be to explore whether there can be a link between the type of nanosystem and its therapeutic or cosmetic use in order to further personalize the therapy. In this review we highlight the main benefits of using nanosystems as reducing dermal toxicity and prolonging the release time of BAK, thus reducing the dose and side effects, as well as having the ability to deliver BAK to deeper layers of the skin. However, both these and other strategies for delivering BAK should be the subject of future research, since the biological properties of BAK are already known. It is therefore necessary to take "better advantage" of these nanosystems in order to increase the bioavailability of BAK and strengthen its dermatological potential, by introducing them into creams, gels, lotions, or other suitable dermal formulations. Assessing the risks of nanosystems and controlling them are fundamental requirements, and this is still a gap. In order to accurately measure toxicity, it is necessary to develop new clinical trials, since most in vitro toxicology studies focus only on one cell line and do not reproduce reality in humans. Nevertheless, it is necessary to create concrete guidelines to confirm the results and develop good models to predict the effect of nanosystems on mammals. In addition, future tests should be performed, both in vitro and in vivo, on damaged skin rather than healthy skin. Once the barrier capacity is compromised, this is reflected in increased permeability, consequently, a variation in pharmacodynamic and pharmacokinetic profiles is expected. In the real skin conditions in which BAK is intended to be applied, the actual skin penetration capacity of these systems, the dwell time and the occurrence of any potential problems they may cause

are not yet fully known. Finally, it is essential to conduct studies to assess and determine the ecotoxicity of these BAK nanosystems more accurately.

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