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Bakuchiol impact on ageing and longevity: Insights from *Caenorhabditis elegans* studies

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Abstract

The efficacy of any herbal medication hinges on delivering adequate levels of plant extract from the therapeutically active phytomolecules. Bakuchiol (BAK), a monoterpenoid derived from *Psoralea corylifolia* with its relevance in cultural and traditional Chinese medicine. Owing to its unique aspects, this molecule has been demonstrated to improve lifespan and antiageing with fewer side effects than synthetic alternatives and easier to use. BAK offers enormous benefits for skin rejuvenation; it acts as a natural retinol alternative, enhancing collagen formation, maintaining skin suppleness and minimizing wrinkles. Furthermore, research conducted on the model organism *Caenorhabditis elegans*, a nematode and prominently one of the primo model systems for ageing research has revealed significant elevation of acetylcholine (Ach) transmission, reduction in reactive oxygen species (ROS) levels and extension of lifespan. Research into the longevity of this model organism using phytomolecules is an intriguing area that explores the potential of leverageing natural compounds derived from plants to prolong the lifespan of this model organism. *C. elegans* has provided valuable insights into the intricate molecular and genetic mechanisms underlying the ageing process. The emerging complex relationship between bakuchiol and *C. elegans* revealed the mechanisms controlling development and lifespan by gently altering longevity genes, particularly those within the mTOR and insulin/IGF-1 signaling pathways, BAK bestowed worms the ability of extended lifespan by promoting cellular renewal. The current study sheds light on its potential to alter cellular pathways linked to longevity and suggest its ability to activate proteins strongly associated with extended lifespans and better health.

1. Introduction

Bakuchiol, a meroterpene within the terpenophenol chemical class, botanical compound extracted from *Psoralea corylifolia* plant gained prominence in skincare and longevity research. Mehta *et al.* (1996) extracted it and its commercial use started in 2007 despite its synthesis in 1973 as sytenol A by Sytheon Ltd. The name bakuchiol originates from Sanskrit term Bakuchi, vital in Indian and Chinese medicine (Chaudhuri *et al*., 2015). Chinese medicine reduced the negative effects of standard cancer therapies and improved quality of life (Husain, 2021). Discovered in 1966, bakuchiol and its analogs are renowned for promoting various biological traits, especially skin rejuvenation and acting as a natural retinol alternative, it enhances collagen production, ensuring firm skin and reducing wrinkles. Medicinal plants generally offer benefits with minimal or no adverse effects. Secondary metabolites like phenolic compounds, terpenoids and polysaccharides in these herbs possess antioxidant and antibacterial properties making them effective for treating various illnesses and disorders (Siddiqui *et al*., 2023). Its antioxidants combat free radicals reduce oxidative stress and protect skin cells crucial for skin health and longevity, countering ageing and age-related issues. Its powerful anti-inflammatory effects are valuable in both skincare and longevity research. Combating chronic inflammation, reducing the risk of age related conditions such as cardiovascular diseases and specific cancers. Ongoing research reveals its potential in modulating cellular pathways associated with longevity shows promise in activating sirtuins proteins tied to extend lifespan and improve health span. Early research suggests its neuroprotective abilities and maintenance of cognitive functions showcasing its multifaceted properties (Krishna *et al*., 2022; Mehta *et al*., 1966).

In 1900, Maupas named the transparent nematode *Rhabditides elegans*. Osche reclassified it as *Caenorhabditis* subgenus in 1952 and Dougherty promoted *Caenorhabditis* to genus status in 1955. This 1 mm long, free-living organism is found in temperate soil environments. *C. elegans*, a tiny 1 mm nematode, serves as a vital model organism in scientific research with an unsegmented pseudocoelomate, lacks respiratory and circulatory systems. It is a hermaphrodite nematode with a bilaterally symmetrical vermiform body. It shares organ systems with larger animals and lacks circulatory and respiratory systems. It has four dorsal and ventral bending muscle bands and a basic nervous system but lacks action potentials and voltage-gated sodium channels (Félix and Braendle, 2010). Its simplicity, genetic tractability and evolutionary similarity to humans make it significant. With 959 transparent somatic cells, it allows detailed *in vivo* observation, aiding cellular level studies. The worms 2-3 days life cycle speed up experiments, especially in genetics and development. Its well annotated genome and ease of genetic manipulation like RNA interference make it an excellent platform for uncovering complex gene functions conserved in humans. The

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synchronized nematode populations ensure reproducible experiments and with its 302-neuron nervous system, it provides a simplified model for neurobiology studies aiding research on neural networks and behavior (Devi, 2021). Its diverse behaviors enable investigations into ageing, stress responses and disease modeling enhancing its use in high-throughput drug screenings. *C. elegans* is a valuable tool for screening plant derived compounds with various biological activities offering insights into ageing related pathways and stress resistance including anticancer, anti-inflammatory, neuroprotective and antiageing properties. Research on antioxidant effects extending lifespan has therapeutic potential for stress related diseases. Studies on natural compounds in this animal model provide crucial data on neuronal health, guiding neuroprotective strategies in humans (Riddle *et al*., 1997). BAK intricate interaction with *C. elegans* reveals pathways controlling longevity and development. It modifies longevity genes including those in the insulin growth factor-1 (IGF-1) and mammalian target of rapamycin (mTOR) pathways, prolonging existence through cellular rejuvenation and influences key pathways like mitogen activated protein kinase (MAPK) cascade and AMP activated protein kinase (AMPK) inducing autophagy, enhancing defenses and strengthening mitochondrial resilience (Husain *et al*., 2018). These interactions lead to observed longevity and developmental benefits in this model system. In *C. elegans* saga, BAK emerges as a protagonist, unraveling lifes mysteries, ageing and existence. Its poetic and profound effect testifies to natural compounds profoundly influence the complex interactions of molecules in life and stands as a beacon in scientific wonder, illuminating the enigmatic intricacies of life tapestry.

2. Natural sources of bakuchiol

Across time, medicinal plants have intrigued humanity offering remedies for health issues and well-being. The primary source of medicine for centuries has been natural sources especially plants due to their affordability, safety and long term use. More than 70% of current drugs are derived from plants and more than 50% of the world's population uses plants for healthcare (Sharma *et al*., 2021). Natural compounds from these plants gain attention in therapeutics due to their perceived lower toxicity and increased tolerability compared to synthetic compounds bridging ancient and modern healing practices. Traditional medicine knowledge offers intrusting leads for pharmacological research (Das *et al.,* 2021). Bakuchiol, an indigenous phytochemical constituent derived from *P. corylifolia* seeds is a meroterpenoid exemplifies this trend. Natural product research involves three main facets: the isolation, the synthesis and the exploration of their biological properties of compounds like BAK, a prime example in this field. Naturally occurring in *P. corylifolia* leaves and seeds, BAK is a botanical mystery with historical significance. Indigenous to India, China and Sri Lanka, this plant part of the Fabaceae family has been used in traditional medicine for centuries. Research shows minimal or negligible negative effects compared to retinoids, positioning as a leading antiageing agent. This evidence suggests its potential for further development, broad application and extensive research endeavors (Krishna *et al*., 2022; Puyana *et al*., 2022). Traditional Chinese and Indian medicine valued BAK for its preventive effects against tumors and inflammation (Figure 1). BAK shows significant antioxidant potential, effectively neutralizing and removing reactive oxygen species (ROS) (Nizam *et al*., 2023). The plant belonging to the Fabaceae family holds a significant place in Indian and Chinese medicinal traditions. While various plants like *Prosopis glandulosa, Otholobium pubescens, Pimelea drupacea, Ulmus davidiana, Piper longum, Aerva sanguinolenta, Fructus psoraleae, Psoralidium tenuiorum, Bridelia retusa, Elaeagnus bockii, Spiraea formosana*, and *Nepeta angustifolia* contain BAK. *P. corylifolia* is the only source capable of providing BAK on a substantial scale. BAK is the predominant compound in *P. corylifolia* constituting about 6.24% of the dried seeds by weight. Additionally, this plant contains various other meroterpenoid compounds (Krishna *et al*., 2022; Puyana *et al*., 2022).

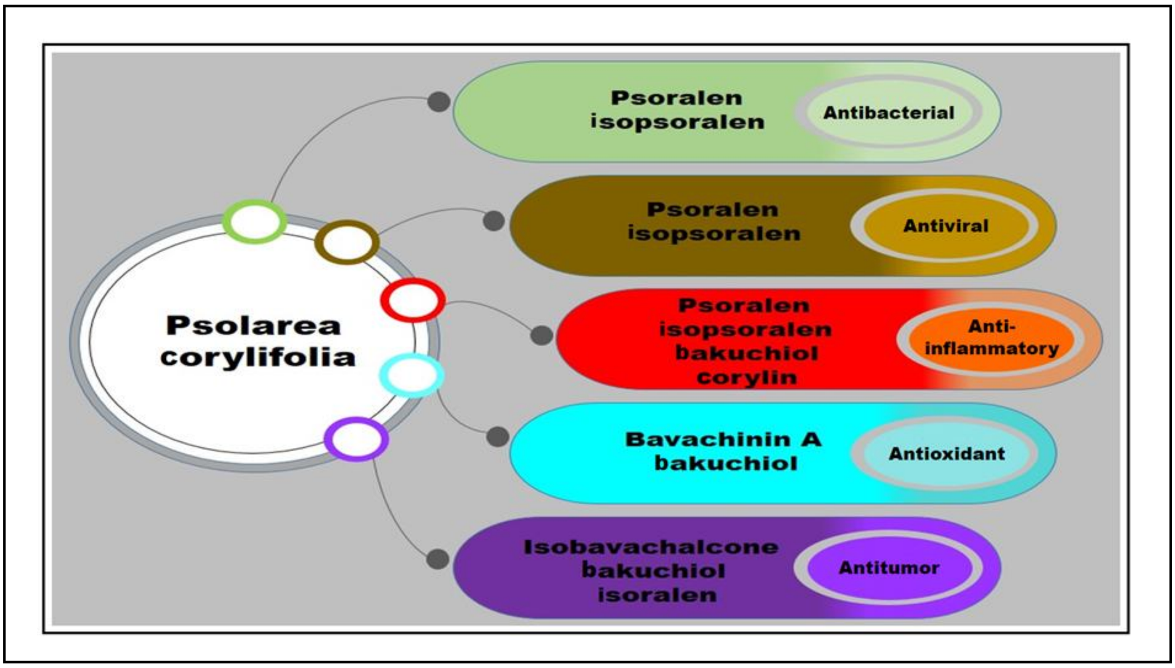

Figure 1: Significant properties possessed by constituents of *Psoralea corylifolia*.

3. Traditional use of *Psoralea corylifolia*

P. corylifolia is identifiable by its dark brown, elongated and smooth surfaced seeds. It primarily grows in the semiarid regions of Rajasthan and eastern districts of Punjab bordering Uttar Pradesh in India. It is also found in various parts of India including the Himalayas, Dehradun and Karnataka. *P. corylifolia* is widely distributed in tropical and subtropical regions including China and Southern Africa. The seeds and oil from this plant have diverse medicinal uses (Figure 2), serving as a diuretic, laxative, stimulant and diaphoretic agent (Annunziato *et al*., 2003). In Chinese traditional medicine, *P. corylifolia* is highly regarded as a tonic herb, known for boosting overall health and vitality. The plants fruit is believed to have aphrodisiac properties and is used as a tonic for genital organs. Additionally, it contains a potent oleoresin with proven efficacy in treating conditions like lumbago and specific kidney ailments (Singh *et al*., 2019). The active fraction from *P. corylifolia* fruits, seeds and roots are rich in flavonoids and meroterpenes displays significant antibacterial, antioxidant and immunomodulatory properties. It is used in the form of ointment or paste both orally and externally to treat inflammatory skin issues such as eczema, leprosy, psoriasis, hair loss and leukoderma (Kumar *et al*., 2023). The methanolic seed extract of this herb was tested *in vitro* showing significant antimycobacterial activity against *Mycobacterium aurum* and *Mycobacterium smegmatis* (Lee *et al*., 2016). Traditional Chinese medicine (TCM) originated in China and spread to Japan, Korea and Vietnam involving acupuncture, moxibustion and herbal medicine (Li *et al*., 2016). Research confirms BAK diverse properties including antitumorigenic, anti-inflammatory, antioxidative, antimicrobial and its potential in combating breast cancer cells, showcasing its anticancer abilities (Nizam *et al*., 2023). Bakuchiol induces S phase arrest and apoptosis in breast cancer cells *via* the mitochondrial pathway. Recent findings also suggest its estrogenic activity *in vitro* and *in vivo*. Further research is necessary to validate BAK potential as an antibreast cancer drug (Li *et al*., 2016). Recent research indicates protective effects on the heart, liver, skin and other organs. BAK treatment safeguards the heart against ischemia-reperfusion injury by modulating cardioprotective pathways. BAK inhibits liver fibrosis by promoting myofibroblast apoptosis, reduces hepatotoxicity by suppressing oxidative stress and inflammation and hampers cancer cell proliferation in the stomach, breast and skin displaying anticancer effects. BAK preserves collagen, slows skin ageing, protects against bone loss with estrogen like effects and delays osteoporosis. It also lowers blood glucose and triglycerides suggesting potential in protecting against pancreatic beta-cell damage and diabetes progression (Li *et al*., 2016). During the viral outbreak, protecting and enhancing our invaluable health is possible through numerous healing plants. Nature has bestowed humanity with diverse plants such as Bakuchi, well documented in Ayurveda, the ancient Indian medical system. Bakuchi seeds exhibit powerful healing qualities addressing diverse health issues. Ayurvedic records emphasize Bakuchi attributes: *Ruchya* (addresses anorexia), *Kushtangna* (treats skin disorders), *Keshya* (enhances hair growth), *Shwasahara* (addresses respiratory issues), *Jwarahara* (treats fevers), *Mehahara* (corrects urinary tract infections), *Vishtambrut* (cures constipation and digestive disorders). Bakuchi seeds contain coumarin, volatile oil, flavones, phenols, lipids and stigma steroids. The oil includes limonene, terpin-4-ol, β-caryophyllene, linalool and geranyl acetate. Medically, bakuchi oil comprises essential components like psoralen, psoralidin, isopsoralen, isopsoralidin, bavacoumestan A, corylidin and bakuchiol. Additionally, Bakuchi has fatty acids palmitic, linoleic and oleic acids with smaller fractions of lignoceric, stearic and linolenic acids (Bakuchi: Health benefits, uses in Ayurveda, formulations, dosage, side effects, 2021).

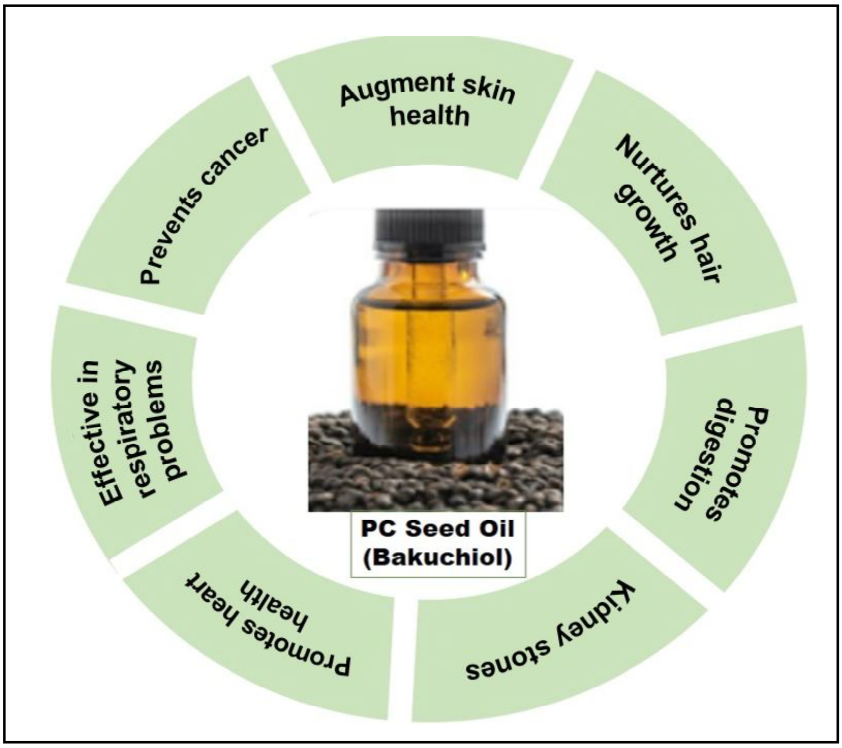

Figure 2: Health benefits of bakuchiol present in seed oil.

4. Chemistry of bakuchiol

Bakuchiol structural and chemical diversity arises from its complex biogenic origin involving isoprene based and amino acid based building blocks in its biosynthetic pathway. BAK aromatic ring comes from the phenyl propane biosynthetic pathway and its monoterpene side chain is derived from the mevalonate pathway (MVA). Isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) labels are evenly distributed. The integration of leucine into bakuchiol involves a process marked by significant randomization. Extracted using methods like solvent and supercritical fluid extraction, its chemical composition is revealed as 1-[(4E,8E)-3,7-dimethyl-9-(3,7,11-trimethyldodeca-2,6,10-trien-1-yl) nona-4,8-dien-1-yl)phenyl) ethanone. Its molecular structure featuring an aromatic core and alkyl side chains enhances its stability and reactivity making it intriguing for chemical investigation. BAK extraction involved cold or hot methods with suitable solvents followed by purification through column chromatography (Figure 3). Alkaline hydrolysis was used to break the lactone ring of furanocoumarins like psoralen and isopsoralen converting them into carboxylic acid salts. These salts were separated from the mixture through aqueous phase separation.

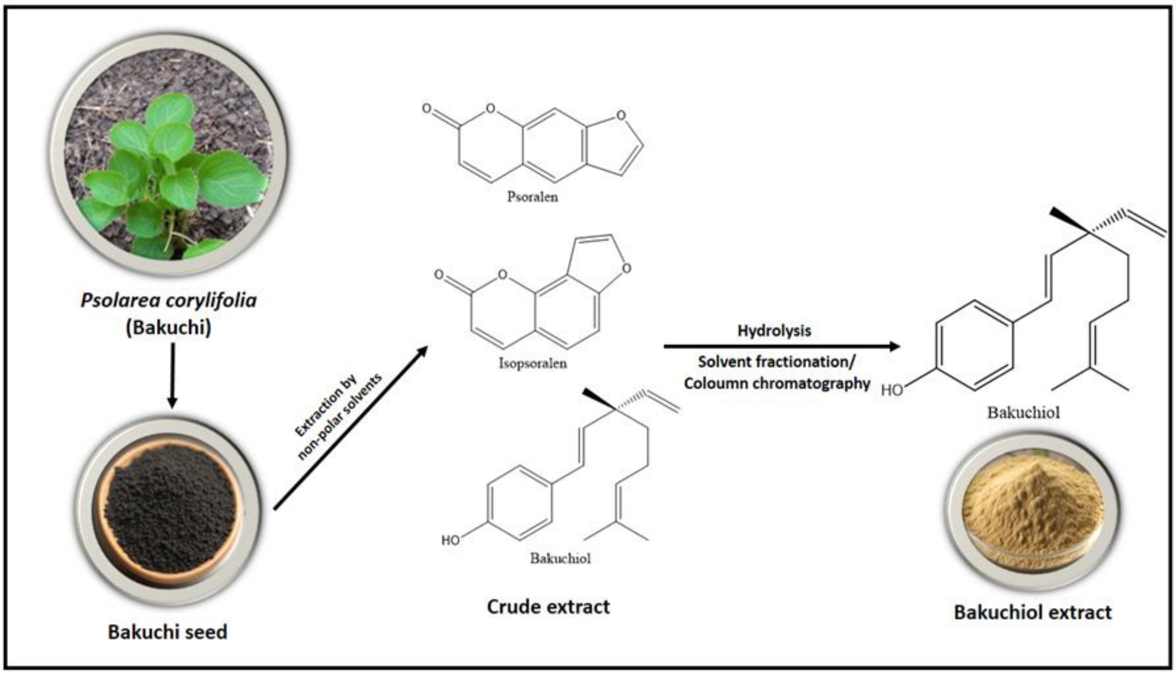

Figure 3: Biosynthesis of bakuchiol.

5. Biological properties of bakuchiol

Derived from *P. corylifolia* bakuchiol exhibits various biological activities such as antitumor, antioxidant, phytotherapeutic, cytotoxic, antimicrobial and hepatoprotective properties. It is also recognized as a topoisomerase II inhibitor. This study explores the development and *in vitro* evaluation of radioiodinated bakuchiol as a potential antitumor agent (Del Río *et al*., 2014). BAK terpenoid component is crucial for its antioxidant effectiveness. It is valuable in formulating antibacterial agents for oral pathogens with applications in food additives and mouthwash for dental caries prevention and treatment. Guided fractionation of *P. corylifolia* extracts isolated BAK along with three other bioactive compounds: cyclobakuchiols A and B, and angelicin, revealing its anti-inflammatory and antipyretic properties. BAK regulates leukocytic processes affecting eicosanoid production, cellular migration and degranulation at inflammatory sites. It mildly inhibits secretory and intracellular phospholipase A2 (PLA2). BAK dose dependently reduces LTB4 synthesis in human neutrophils and TXB2 in platelet microsomes. It also suppresses the inducible nitric oxide synthase gene expression by deactivating nuclear transcription factor kappa B in RAW 264.7 macrophages. BAK inhibits mitochondrial lipid peroxidation and has been isolated from *Otholobium pubescens* (Fabaceae) for antihyperglycemic effects. The BuguZhi agent, containing bakuchiol and other coumarin type compounds aids bone healing. However, its use is limited due to scarcity in natural sources and potential presence of toxic components. A significant concern with BAK compositions from the *Psoralea* genus is the presence of psoralens, particularly psoralen and isopsoralen. These furanocoumarins are natural secondary metabolites found in plants including fruits and vegetables (Del Río *et al*., 2014). BAK gentle yet powerful properties have transformed the cosmetic industry by providing a solution for sensitive skin. It promotes collagen production, reduces fine lines and rejuvenates the skin without the irritation of traditional retinoids. Its antimicrobial and anti-inflammatory qualities have also driven innovations in dermatological treatments, demonstrating its potential in addressing skin disorders. In the field of medicine, BAK therapeutic potential is undergoing extensive exploration. BAK anti-inflammatory and antioxidant properties are being utilized to create treatments for chronic inflammatory diseases like arthritis and inflammatory bowel diseases offering a natural approach to manage these conditions. Its neuroprotective effects are under scrutiny, suggesting potential applications in preventing and treating neurodegenerative disorders like Alzheimer's and Parkinson's diseases. These developments represent a shift in conventional medicine, integrating the potency of natural compounds for improved therapeutic outcomes. In the field of longevity studies, BAK has become a game changer as in one of the studies BAK treatment remarkably extended the lifespan both in wild-type worms and Aβ worms. This finding not only demonstrated the pro-longevity impact of BAK in worms but also highlighted the intriguing idea that BAK may be useful as an anti-AD treatment (Ranjan *et al*., 2023). Researchers explore BAK potential in ageing related pathways like sirtuin and AMP-activated protein kinase (AMPK) signaling, hinting at prolonged lifespan and improved health span. This offers exciting prospects in antiageing research, advancing our understanding of molecular ageing processes.

5.1 An alternative to retinol

BAK, a plant-based antiageing ingredient gains popularity. Despite structural differences from retinol, Chaudhuri and Bojanowski (2014) research shows similar antiageing gene and protein expression. BAK, distinct from retinol, provides excellent stability, safety and easy formulation with diverse emollients and solubilizers. BAK, a day friendly retinol stabilizer with antioxidant properties requires no skin sensitization or gradual adaptation, making it pregnancy-safe. These qualities contribute to BAK increasing popularity in cosmetics (Chaudhuri and Bojanowski, 2014; Wysocka, n.d.). In a 2020 study, a serum with bakuchiol and vanilla tahitensis improved skin firmness reduced deformation and protected against UVA damage. BAK alone minimized dullness, promoting brightness and hydration. Compared to retinol, bakuchiol rich in antioxidants, aids safer and more effective epidermal regeneration combating skin ageing (Wells and Sands, 2022). Retinol and BAK affects gene expression similarly. The side-by-side analysis of gene regulation, ELISA and histochemistry protein levels verified these shared characteristics. DNA microarray analysis demonstrated retinol like activity for up regulating types I and IV collagen and stimulating type III collagen in the mature fibroblast model. In a clinical case study, BAK was used as a skincare product twice daily on the face. After 12 weeks of treatment, lines, wrinkles, pigmentation, elasticity, firmness and photo damage improved without the side effects of retinol therapy. Clinical investigation indicating topical 0.5% bakuchiol improves clinical appearance (% improvement vs. baseline) of photo-aged/naturally aged skin (Chaudhuri and Bojanowski, 2014). BAK caused less stinging and scaling than retinol in one investigation (Dhaliwal *et al*., 2019). In addition BAK enhances human skin fibroblast (ESF-1) cell activity, promote collagen and matrix metalloproteinase inhibitors mRNA expression level and inhibit mRNA expression of matrix metalloproteinases in order to postpone skin ageing (Yu *et al*., 2014). BAK, thus appears to be a promising alternative to retinol for facial antiageing treatments (Dhaliwal *et al*., 2019; Sadgrove *et al*., 2021).

5.2 Importance of bakuchiol in *C. elegans*

5.2.1 Ageing and longevity effects of BAK studied in *C. elegans*

According to literature (Ranjan *et al*., 2023), bakuchiol has been shown to significantly reduce ROS levels and extend longevity in model organisms *C. elegans*. Natural phytochemicals with antiageing characteristics have fewer adverse effects than synthetics, making them easier to regulate for human usage (Pandey and Chauhan, 2021). Plant derived phytochemicals which are essential bioactive substances offer potential for prolonging longevity according to screening in *C. elegans* (Ye *et al*., 2014). Plants and byproducts are being intensively studied for health promoting chemicals (Kumar *et al*., 2015; Mohd Sahardi and Makpol, 2019). BAK has been shown in many trials to have protective effects on important organs (Xin *et al*., 2019). BAK mimics estrogen actions (Lim *et al*., 2011; Weng *et al*., 2015). Estrogens are strong neuroprotectants protecting against oxidative stress, mitochondrial damage, neuroinflammation, neurodegeneration and other CNS injury processes (Engler-Chiurazzi *et al*., 2017; Miller and Duckles, 2008; Villa *et al*., 2016). More than 70 genes involved in processes influencing *C. elegans* longevity have been found with the possibility of more discoveries. Thus, like other phytomolecules BAK has antiageing and longevity benefits in *C .elegans* (Ranjan *et al*., 2023).

5.2.2 Health parameters enhancements in *C. elegans*

In *C. elegans,* essential parameters for studying lifespan and ageing effects include oxidative stress resistance and mobility. Oxidative stress, a significant ageing factor is associated with the pathogenesis of various diseases (Senchuk *et al*., 2017). Naturally occurring phytomolecules in plants display diverse bioactive properties influencing health. In *C. elegans* these compounds have been noted to improve oxidative stress resistance and mobility.

5.2.3 Oxidative stress resistance

BAK act as antioxidants combating oxidative stress. Studies show they enhance *C. elegans* resistance to oxidative stress, mitigating the harmful impact of ROS on cells and tissues (Adhikari *et al*., 2003; Liu *et al*., 2020; Nizam *et al*., 2023; Rodriguez *et al*., 2013).

5.2.4 Mobility

Preserving mobility is key for healthy ageing (Rantakokko *et al*., 2013). Some studied phytomolecules in *C. elegans* show potential in enhancing mobility indicating a protective effect on muscle tissues and overall neuromuscular function. In *C. elegans* studies, compounds are evaluated for impacts on oxidative stress resistance and mobility aiding ageing process understanding. Positive changes may reveal potential antiageing effects. BAK treatment in *C. elegans* shows enhanced oxidative stress resistance and mobility (Ranjan *et al*., 2023) suggesting effects on ageing-related health. Valuable findings provide insights generate hypotheses for further exploration.

5.3 Mechanisms underlying bakuchiol effects

5.3.1 Antioxidant activity

Introduced by Sydney Brenner in the 1970, *C. elegans* is a crucial model for studying ageing, oxidative stress, neurodegeneration and inflammation due to its high homology with human pathways. This makes it promising for exploring the effects of phytochemicals on mechanisms related to excessive ROS production which damages cell structures such as lipids, proteins and DNA (Valko *et al*., 2007). Harman (1956) suggested ageing results from free radical induced oxidative damage (Harraan, 1955). Cells manage ROS levels *via* endogenous mechanisms with antioxidants (*e.g.*, glutathione) and enzymes (*e.g.,* SOD, GPO, CAT) (Sies, 1993). Dietary antioxidants (*e.g.,* vitamins E and C) and phytomolecules regulate ROS levels addressing oxidative stress (Halliwell, 2011). These compounds efficiently scavenge oxidizing species stabilizing radicals through hydrogen atom or single electron transfer (Bors *et al*., 1990). They also chelate redox active metal ions like Fe^{2+} or Cu^{2+} preventing

Fenton like reactions and reducing the production of oxidant species (Leopoldini *et al*., 2011). *In vivo*, they potentially facilitate indirect antioxidant mechanisms by inhibiting pro-oxidant enzymes recycling α-tocopheroxyl radicals at lipid water interfaces (Mazza *et al*., 2008) or activating natural antioxidant defenses (Barrajón-Catalán *et al*., 2014). *C. elegans* with high genetic homology to humans is a valuable model for studying natural compound activity in ageing, apoptosis, signaling, metabolism and cell cycle processes (Guarente and Kenyon, 2000; Kyriakakis *et al*., 2015). Its insulin/IGF-1 signaling pathway (IIS) is pivotal in the oxidative stress response. ILPs binding to DAF-2, the IGFR homolog (Mohri-Shiomi and Garsin, 2008) activates a cascade involving serine/threonine kinases (AGE-1/PI3K, PDK-1, AKT-1/2, SGK-1) phosphorylating transcription factors (DAF-16/FoxO, HSF-1, SKN-1/Nrf) inhibiting their nuclear translocation and activity. DAF-18/PTEN lipid phosphatase opposes AGE-1/PI3K signaling preventing phosphorylation and cytoplasmic sequestration (Murphy and Hu, 2018). Inhibiting the DAF-2 pathway promotes nuclear translocation of DAF-16, HSF-1 and SKN-1 influencing gene expression related to longevity, stress response, metabolism and protein processes. Affected genes include catalase (ctl-1), superoxide dismutase-3 (sod-3), metallothionein (mtl-1), bacterial defense genes (lys-7, spp-1), molecular chaperones (*e.g.,* hsp-16.2) and glutathione S-transferase (gst-4) (Hsu *et al*., 2003; Murphy and Hu, 2018). HSF-1 binds DNA with heat shock elements (HSE) inducing chaperone genes (HSP-16, HSP-70) for *C. elegans* longevity and thermotolerance. Mutant worms in stress or ageing genes offer insights into phytochemical antioxidant effects. BAK lowers ROS in *C. elegans* (Miao *et al*., 2018). HSF-1, vital for proteotoxicity mitigation, lifespan regulation and autophagy activates heat shock proteins like hsp-70 and hsp-16.2 (Gomez-Pastor *et al*., 2018; Prahlad *et al*., 2008). BAK treatment significantly boosts mRNA expression of hsf-1 (human HSF1 ortholog) and lgg-1 (GABA type a receptor-associated protein).

5.3.2 Longevity mechanism

Ageing involves a gradual decline across levels leading to disease and death (Booth and Brunet, 2016; Sen *et al*., 2016). Mutations in the insulin/IGF-1 receptor extend lifespan in *C. elegans*, rodents and fruit flies (Blüher *et al*., 2003; Holzenberger *et al*., 2003; Kenyon *et al*., 1993; Kimura *et al*., 1997a; Tatar *et al*., 2003) emphasizing the crucial role of genetic factors tied to metabolic regulation and nutrition (Kenyon, 2011). This insight provided a significant molecular view on longevity. Initially, ageing was not considered a regulated process. The discovery of the insulin/IGF-1 signaling pathways role in regulating lifespan in *C. elegans* was groundbreaking reshaping our understanding of ageing (Uno and Nishida, 2016). Overall, natural product research is a vigorous tool to discover novel biological active compounds with unique mode of action (Arif *et al*., 2022)

5.4 Molecular and cellular mechanisms through which BAK influences *C. elegans*

Ongoing investigations are delving into the effects of BAK on the cellular mechanisms of *C. elegans*. Although, the specific mechanisms are yet to be fully unveiled, potential ways in which BAK influences cellular processes are actively being explored.

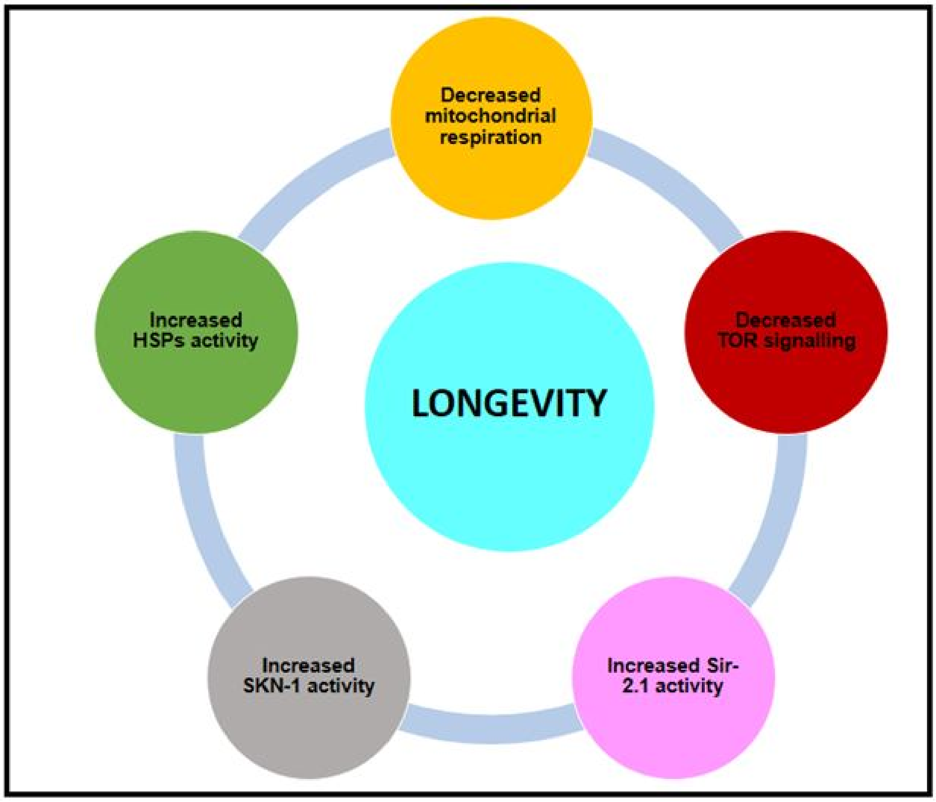

Figure 4: Increased/Decreased cellular signaling response promoting longevity in *C. elegans*

5.4.1 SIRT1 pathway

SIRT1 is among the most investigated mammalian sirtuins (SIRT) as it was the first NAD+ dependent deacetylase and the mammalian ortholog of Sir2, a protein encoded by the silent information regulator 2 (Sir2) gene (Imai *et al*., 2000; Landry *et al*., 2000). Increased SIRT1 expression extends yeast, *C. elegans* and mouse lifespans (Chen *et al*., 2020). Multiple studies shown that boosting SIRT1 expression, protein levels and activity or augmenting its activity by allosteric interaction can extend life and cure numerous age related illnesses (Bonkowski and Sinclair, 2016; Dai *et al*., 2018; Iside *et al*., 2020; Wang *et al*., 2019). Monoterpenoids, among other natural and synthetic SIRT1 activators can improve several pathological diseases by increasing SIRT1 activity. BAK induces SIRT1expression (Feng *et al*., 2016; Ma *et al*., 2020). Sirtuin interacts with insulin/IGF-1, AMP-activated protein kinase and forkhead box O signalling pathways to regulate longevity.

5.4.2 AMPK pathway

Efficient regulation of energy metabolic balance, increased stress tolerance and qualified cellular housekeeping are the characteristics of better health and longevity. AMPK signalling regulates all of these properties *via* an integrated signalling network. Furthermore, AMPK induced activation of the FoxO/DAF-16, Nrf2/SKN-1 and SIRT1 signalling pathways enhance cellular stress resistance. Model organism studies have demonstrated that mammalian AMPK and its *C. elegans* orthologue, AMP-activated kinase-2 (AAK-2) play an important role in the control of lifespan. *C. elegans* longevity is extended by overexpressing AAK-2/AMPK and activating it with metformin (Apfeld *et al*., 2004; Curtis *et al*., 2006; Onken and Driscoll, 2010). BAK reduces oxidative stress and apoptosis *via* controlling the activation of AMPK (Salminen and Kaarniranta, 2012).

5.4.3 mTOR pathway

The conserved serine/threonine protein kinase mechanistic target of rapamycin (mTOR) integrates several extracellular and intracellular inputs including nutrients and growth stimuli. Impaired mTOR signalling has been linked to a variety of age related diseases including diabetes, cancer and neurodegeneration as well as ageing. The crucial role of mTOR in ageing was originally discovered in invertebrate creatures where reduction of mTOR components was found to enhance longevity. mTOR signalling affects essential cellular processes such as autophagy, cell proliferation, protein translation and targeting these pathways impacts ageing and health in model organisms (Lamming *et al*., 2021). Experiments with the nematode *C. elegans* provided the first evidence that mTOR regulates longevity (Vellai *et al*., 2003). In this hypothesis, the mTOR and DAF-2/IGF signalling pathways may be associated to ageing, metabolism and reproductive growth (Kenyon *et al*., 1993; Kimura *et al*., 1997b; Vellai *et al*., 2003). BAK, which has antiageing properties and increases lifespan (Ranjan *et al*., 2023) may also have an effect on this pathway.

5.4.4 Nrf2 signalling

The multifunctional regulator nuclear factor erythroid 2 related factor (Nrf2) is regarded not only a cytoprotective factor that regulates the expression of genes coding for antioxidant, anti-inflammatory and detoxifying proteins, but it is also a strong modulator of species lifespan (Figure 5) (Loboda *et al*., 2016).

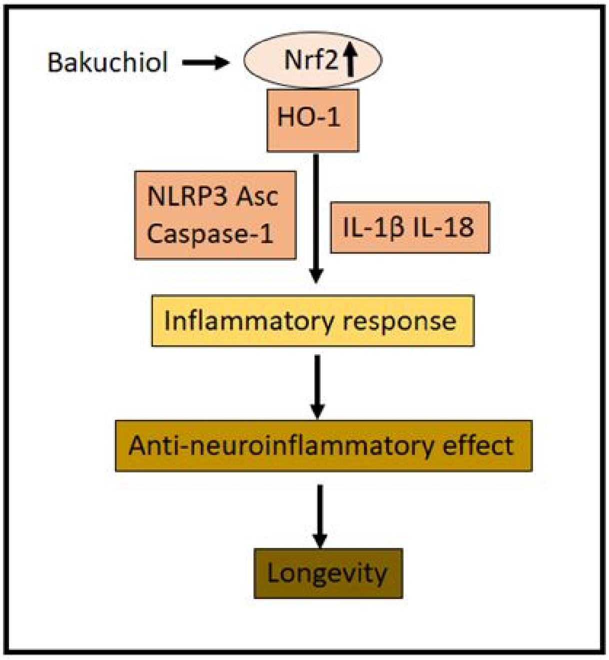

Figure 5: BAK role in antineuroinflammation *via* Nrf 2 signalling.

BAK exert anti-inflammatory effects via stimulating Nrf2 signalling. The nucleotide binding domain (NOD) leucine rich containing family, pyrin domain containing-3(NLRP3) is a major inflammasome that consists mostly of the NOD like receptor protein NLRP3, the adaptor protein apoptosis associated speck like protein (ASC) and caspase-1. Ischemic stroke can activate NLRP3 which regulates caspase-1 activation to generate mature precursor cytokines including pro-inflammatory interleukin-1β (IL-1β) and IL-18 resulting in cell death and extravasation. Furthermore, the activation of the nuclear factor erythroid 2 like 2 (Nrf2) pathway is closely connected with inflammation (Xu *et al*., 2021). Studies on neurodegenerative disorders such as AD, PD, Amyotrophic lateral sclerosis, Huntington's disease and others have shown that inflammation is not just a by product of neurodegeneration but also a critical factor in the process (Kip and Parr-Brownlie, 2022; Wyss-Coray, 2016; Zhang *et al*., 2023). The skn-1 gene in *C. elegans* encodes a transcription factor similar to human Nrf2 that triggers a detoxifying response. skn-1 enhances tolerance to oxidative damage and extends longevity (Tullet *et al*., 2017).

5.5 Earlier studied common terpenes in *C. elegans* for antiageing effects

C. elegans is an excellent antiageing model utilized for screening natural bioactive substances. Plant derived micronutrients are employed with polyphenols, among 30 effective antiageing substances, particularly intriguing for preventing degenerative diseases and modifying the ageing process (Liu *et al*., 2021).

Table 1: List of some terpenoids impacting *C. elegans*

S. No.	Terpenoids	Plant source	Implicated bio-marker genes	Pathway	Antiageing effect	References
1.	Limonenes	Citrus plants	Igf ,daf-16,ho-1	IIS (Insulin/IGF-1 signaling)	Antioxidant	Shukla *et al*., 2019; Tang *et al*., 2019
2.	Beta-caryo-phyllene	Essential oil of Cannabis, Clove, oregano, *Ocimum basilicum*	mev-1, daf-16	IIS	Dietary restriction, Modulation of cellular stress response	Pant *et al*., 2014
3.	Specioside	*Stereospermum suaveolens*	mev-1, sod-1, sod-2, sod-3, *hsp*-16.2, *hsp*-70 and gst-4	IIS	Antioxidant, stress resistant	Asthana *et al*., 2015
4.	Carvacrol and thymol	Essential oil	sod-3, gst -4	DAF-16/FOXO	Antioxidant	Fuentes *et al*., 2022
5.	4-Hydroxy-E-globularinin (4-HEG)	*Premna integrifolia*	hsp-16.2 and sod-3	DAF-16/FOXO	Antioxidant, decrease lipid level	Shukla *et al*., 2012
6.	Paeoniflorin	*Paeonia lactiflora*	Bcl2,	Akt/GSK-3β s	Antioxidant, anti -inflammatory, and antiapoptotic	Wojtunik-Kulesza *et al*., 2021
7.	Catalpol	Rehmannia glutinosa (Chinese foxglove)	mek-1, daf 2, age -1,daf-16 and skn-1	IIS	Antioxidant, Anti-Alzheimer's, Anti-Parkinson's, Antistroke	Liu *et al*., 2006; Wang *et al*., 2014
8.	Ferruginol	*Cryptomeria japonica* (Sugi wood)	sod-3, gst 4	IIS	Antioxidant, decrease Aβ toxicity	Hadipour, 2024; Ranjan *et al*., 2023
9.	Oleuropein aglycone	*Olive oil*	sirt-1, daf-16	AMPK	Antioxidant, decrease Aβ toxicity	Wojtunik-Kulesza *et al*., 2021
10.	Quinic acid	*Uncaria tomentosa* (Cat's Claw)	hsp-16.2, daf-16	DAF-16/FOXO	Antioxidant	Zhang *et al*., 2012

6. Challenges and future directions

BAK offers potential health advantages including as lifespan, antioxidant qualities, antiageing effects in cosmetics and the ability to address ageing and oxidative stress related illnesses. The study implies that knowing the influence of BAK on people might help with personalised therapy, which focuses on distinct genetic composition and lifestyles. BAK ability to counteract ROS levels associated with lifespan is endorsed by its modulation of stress responsive and mitochondrial genes. Despite minimal studies, it may increase longevity and improve general well-being. Bakuchiol research is hampered by a lack of human investigations, substantial clinical trials and long term safety testing. Continuous research is required to assess effectiveness, possible adverse effects and long term user safety. Research on BAK metabolism and bioavailability is limited, prompting more research to better understand its effects on the human body. Its possible applications include treating osteoporosis and controlling disorders like down syndrome. More study is needed to better understand its processes in ageing and how it affects other organs and disorders.

7. Conclusion

In *C. elegans* saga, BAK emerges as a protagonist, unraveling life's mysteries, ageing and existence. Its poetic and profound effect testifies to natural compounds profoundly influence the complex interactions of molecules in life and stands as a beacon in scientific wonder, illuminating the enigmatic intricacies of life's tapestry. Our understanding of the molecular and genetic mechanisms underlying ageing and these findings may have implications for human health and longevity. Research in this area contributes how BAK may promote healthy ageing and provides a foundation for developing interventions that could extend lifespan and improve the overall quality of life in the ageing population.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

References

Adhikari, S.; Joshi, R.; Patro, B. S.; Ghanty, T. K.; Chintalwar, G. J.; Sharma, A. and Mukherjee, T. (2003). Antioxidant activity of bakuchiol: Experimental evidences and theoretical treatments on the possible involvement of the terpenoid chain. Chemical Research in Toxicology, **16**(9):1062-1069.

Annunziato, L.; Amoroso, S.; Pannaccione, A.; Cataldi, M.; Pignataro, G.; D'Alessio, A.; Sirabella, R.; Secondo, A.; Sibaud, L.and Di Renzo, G. F. (2003). Apoptosis induced in neuronal cells by oxidative stress: Role played by caspases and intracellular calcium ions. Toxicology Letters, **139**(2-3):125-133.

Apfeld, J.; O'Connor, G.; McDonagh, T.; DiStefano, P. S. and Curtis, R. (2004). The AMP-activated protein kinase AAK-2 links energy levels and insulin-like signals to lifespan in *C. elegans*. Genes and Development, **18**(24):3004-3009.

Arif, S.; Sharma, A. and Islam H. M. (2022). Plant derived secondary metabolites as multiple signaling pathways inhibitors against cancer. Ann. Phytomed., **11**(1):189-200.

Asthana, J.; Yadav, A. K.; Pant, A.; Pandey, S.; Gupta, M. M. and Pandey, R. (2015). Specioside ameliorates oxidative stress and promotes longevity in *Caenorhabditis elegans*. Comparative Biochemistry and Physiology Part C: Toxicology and Pharmacology, **169**:25-34.

Bakuchi: Health benefits, uses in Ayurveda, formulations, dosage, side effects. (2021).

Barrajón-Catalán, E.; Herranz-López, M.; Joven, J.; Segura-Carretero, A.; Alonso-Villaverde, C.; Menéndez, J. A. and Micol, V. (2014). Molecular promiscuity of plant polyphenols in the management of age-related diseases: Far beyond their antioxidant properties. In: J. Camps (Ed.), Oxidative stress and inflammation in non-communicable diseases-Molecular mechanisms and perspectives in therapeutics, **824**:141-159. Springer International Publishing.

Blüher, M.; Kahn, B. B. and Kahn, C. R. (2003). Extended longevity in mice lacking the insulin receptor in adipose tissue. Science, **299**(5606):572-574. https://doi.org/10.1126/science.1078223

Bonkowski, M. S. and Sinclair, D. A. (2016). Slowing ageing by design: The rise of NAD+ and sirtuin-activating compounds. Nature Reviews Molecular Cell Biology, **17**(11):679-690.

Booth, L. N. and Brunet, A. (2016). The ageing epigenome. Molecular Cell, **62**(5):728-744.

Bors, W.; Heller, W.; Michel, C. and Saran, M. (1990). Flavonoids as antioxidants: Determination of radical-scavenging efficiencies. In: Methods in Enzymology, **186**:343-355.

Chaudhuri, R. K. and Bojanowski, K. (2014). Bakuchiol: A retinol-like functional compound revealed by gene expression profiling and clinically proven to have antiageing effects. International Journal of Cosmetic Science, **36**(3):221-230.

Chaudhuri, R. K.; Sivamani, R.; Jagdeo, J. R.; Elsner, P.and Maibach, H. I. (2015). Bakuchiol: A retinol-like functional compound, modulating multiple retinol and non-retinol targets. Cosmeceuticals and Active Cosmetics. 3rd Ed. Boca Raton: Taylor and Francis Group. pp:1-8.

Chen, C.; Zhou, M.; Ge, Y. and Wang, X. (2020). SIRT1 and ageing related signaling pathways. Mechanisms of Ageing and Development, **187**:111215.

Curtis, R.; O'Connor, G. and DiStefano, P. S. (2006). Ageing networks in *Caenorhabditis elegans*: AMP activated protein kinase (*aak 2)* links multiple ageing and metabolism pathways. Ageing Cell, **5**(2):119-126. https://doi.org/10.1111/j.1474-9726.2006.00205.

Dai, H.; Sinclair, D. A.; Ellis, J. L. and Steegborn, C. (2018). Sirtuin activators and inhibitors: Promises, achievements and challenges. Pharmacology and Therapeutics, **188**:140-154.

Das, P.; Preethi,K.; Kiruba, A. A.; Nikhil,K. and Nayak, A. (2021). Flavonoids: An alternative pathway for the treatment of Alzheimer's disease. Ann. Phytomed., **10**(2):240-251.

Del Río, J. A.; Díaz, L.; García-Bernal, D.; Blanquer, M.; Ortuno, A.; Correal, E. and Moraleda, J. M. (2014). Furanocoumarins: Biomolecules of therapeutic interest. Studies in Natural Products Chemistry, **43**:145-195.

Devi, G. (2021). Biological model: *Caenorhabditis elegans*. Int. J. Curr. Microbiol. App. Sci., **10**(05):230-235.

Dhaliwal, S.; Rybak, I.; Ellis, S. R.; Notay, M.; Trivedi, M.; Burney, W.; Vaughn, A. R.; Nguyen, M.; Reiter, P.and Bosanac, S. (2019). Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing. British Journal of Dermatology, **180**(2):289-296.

Engler-Chiurazzi, E. B.; Brown, C. M.; Povroznik, J. M. and Simpkins, J. W. (2017). Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive ageing and brain injury. Progress in Neurobiology, **157**:188-211.

Félix, M. A. and Braendle, C. (2010). The natural history of *Caenorhabditis elegans*. Current Biology, **20**(22):965-969.

Feng, J.; Yang, Y.; Zhou, Y.; Wang, B.; Xiong, H.; Fan, C.; Jiang, S.; Liu, J.; Ma, Z.; Hu, W.; Li, T.; Feng, X.; Xu, J. and Jin, Z. (2016). Bakuchiol attenuates myocardial ischemia reperfusion injury by maintaining mitochondrial function: The role of silent information regulator 1. Apoptosis, **21**(5):532-545.

Fuentes, C.; Verdú, S.; Fuentes, A.; Ruiz, M. J. and Barat, J. M. (2022). Effects of essential oil components exposure on biological parameters of *Caenorhabditis elegans*. Food and Chemical Toxicology, **159**: 112763.

Gomez-Pastor, R.; Burchfiel, E. T. and Thiele, D. J. (2018). Regulation of heat shock transcription factors and their roles in physiology and disease. Nature Reviews Molecular Cell Biology, **19**(1):4-19.

Guarente, L. and Kenyon, C. (2000). Genetic pathways that regulate ageing in model organisms. Nature, **408**:255-262.

Hadipour, E.; Shahangian, S. S. and Mashayekhi, F. (2024). Monoterpenes and diterpenes in combating Alzheimer disease, mechanisms and clinical insights: A comprehensive review. Caspian J. Neurol. Sci., **10**(1):1-19.

Halliwell, B. (2011). Free radicals and antioxidants-quo vadis? Trends in Pharmacological Sciences, **32**(3):125-130.

Harraan, D. (1955). Ageing: A theory based on free radical and radiation chemistry.

Holzenberger, M.; Dupont, J.; Ducos, B.; Leneuve, P.; Géloën, A.; Even, P. C.; Cervera, P. and Le Bouc, Y. (2003). IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature, **421**(6919):182-187.

Hsu, A.-L.; Murphy, C. T. and Kenyon, C. (2003). Regulation of ageing and age-related disease by DAF-16 and heat shock factor. Science, 300(5622):1142-1145. https://doi.org/10.1126/science. 1083701

Husain, F. M.; Ahmad, I.; Khan, F. I.; Al-Shabib, N. A.; Baig, M. H.; Hussain, A.; Rehman, M. T.; Alajmi, M. F. and Lobb, K. A. (2018). Seed extract of *Psoralea corylifolia* and its constituent bakuchiol impairs AHL-based quorum sensing and biofilm formation in food-and human-related pathogens. Frontiers in Cellular and Infection Microbiology, pp:8-351.

Husain, K. M. (2021). Herbs that heal: Relevance of traditional natural remedies in promotion of health. Ann. Phytomed., **10**(2):4-21.http://dx.doi.org/10.21276/ap.2021.10.2.2.

Imai, S.; Armstrong, C. M.; Kaeberlein, M. and Guarente, L. (2000). Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature, 403(6771):795-800.

Iside, C.; Scafuro, M.; Nebbioso, A. and Altucci, L. (2020). SIRT1 activation by natural phytochemicals: An overview. Frontiers in Pharmacology, 11:1225.

Kenyon, C. (2011). The first long-lived mutants: Discovery of the insulin/IGF-1 pathway for ageing. Philosophical Transactions of the Royal Society B: Biological Sciences, 366(1561):9-16.

Kenyon, C.; Chang, J.; Gensch, E.; Rudner, A. and Tabtiang, R. (1993). A *C. elegans* mutant that lives twice as long as wild type. Nature, 366(6454):461-464.

Kimura, K. D.; Tissenbaum, H. A.; Liu, Y. and Ruvkun, G. (1997a). Daf-2, an insulin receptor like gene that regulates longevity and diapause in *Caenorhabditis elegans*. Science, 277(5328):942-946.

Kimura, K. D.; Tissenbaum, H. A.; Liu, Y. and Ruvkun, G. (1997b). Daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. Science, 277(5328):942-946.

Kip, E. and Parr-Brownlie, L. C. (2022). Reducing neuroinflammation via therapeutic compounds and lifestyle to prevent or delay progression of Parkinson's disease. Ageing Research Reviews, 78:101618.

Krishna, T. A.; Edachery, B. and Athalathil, S. (2022). Bakuchiol-a natural meroterpenoid: Structure, isolation, synthesis and functionalization approaches. RSC Advances, 12(14):8815-8832.

Kumar, A.; AlGhamdi, K. M.; Khan, A. A.; Ahamad, R.; Ghadeer, A. and Bari, A. (2023). *Psoralea corylifolia* (Babchi) seeds enhance proliferation of normal human cultured melanocytes: GC-MS profiling and biological investigation. Open Chemistry, 21(1):20220292. https://doi.org/10.1515/chem-2022-0292

Kumar, J.; Park, K. C.; Awasthi, A. and Prasad, B. (2015). Silymarin extends lifespan and reduces proteotoxicity in *C. elegans* Alzheimer's model. CNS and Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS and Neurological Disorders), 14(2):295-302.

Kyriakakis, E.; Markaki, M. and Tavernarakis, N. (2015). *Caenorhabditis elegans* as a model for cancer research. Molecular and Cellular Oncology, 2(2):975027. https://doi.org/10.4161/23723556.2014.975027

Lamming, D.; Houtkooper, R. and Bakula, D. (2021). The critical role of mTOR in longevity and ageing regulation. Reviews, pp:1033.

Landry, J.; Sutton, A.; Tafrov, S. T.; Heller, R. C.; Stebbins, J.; Pillus, L. and Sternglanz, R. (2000). The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. Proceedings of the National Academy of Sciences, 97(11):5807-5811. https://doi.org/10.1073/pnas.110148297

Lee, Y.; Jun, H. S. and Oh, Y. S. (2016). Protective effect of *Psoralea corylifolia* L. seed extract against palmitate-induced neuronal apoptosis in PC12 cells. Evidence-Based Complementary and Alternative Medicine, 2016.

Leopoldini, M.; Russo, N. and Toscano, M. (2011). The molecular basis of working mechanism of natural polyphenolic antioxidants. Food Chemistry, 125(2):288-306.

Li, L.; Chen, X.; Liu, C. C.; Lee, L. S.; Man, C. and Cheng, S. H. (2016). Phytoestrogen bakuchiol exhibits *in vitro* and *in vivo* antibreast cancer effects by inducing S phase arrest and apoptosis. Frontiers in Pharmacology, 7:128.

Lim, S. H.; Ha, T. Y.; Ahn, J. and Kim, S. (2011). Estrogenic activities of *Psoralea corylifolia* L. seed extracts and main constituents. Phytomedicine, 18(5):425-430.

Liu, H.; Guo, W.; Guo, H.; Zhao, L.;Yue, L.; Li, X.; Feng, D.; Luo, J.; Wu, X. and Cui, W. (2020). Bakuchiol attenuates oxidative stress and neuron damage by regulating Trx1/TXNIP and the phosphorylation of AMPK after subarachnoid hemorrhage in mice. Frontiers in Pharmacology, 11:712.

Liu, J.; He, Q.J.; Zou, W.; Wang, H.X.; Bao, Y.M.; Liu, Y. and An, L.J. (2006). Catalpol increases hippocampal neuroplasticity and up-regulates PKC and BDNF in the aged rats. Brain Research, 1123(1):68-79.

Liu, L.; Guo, P.; Wang, P.; Zheng, S.; Qu, Z. and Liu, N. (2021). The review of antiageing mechanism of polyphenols on *Caenorhabditis elegans*. Frontiers in Bioengineering and Biotechnology, 9:635768.

Loboda, A.; Damulewicz, M.; Pyza, E.; Jozkowicz, A. and Dulak, J. (2016). Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: An evolutionarily conserved mechanism. Cellular and Molecular Life Sciences, 73:3221-3247.

Ma, W.; Guo, W.; Shang, F.; Li, Y.; Li, W.; Liu, J.; Ma, C. and Teng, J. (2020). Bakuchiol alleviates hyperglycemia-induced diabetic cardiomyopathy by reducing myocardial oxidative stress *via* activating the SIRT1/Nrf2 signaling pathway. Oxidative Medicine and Cellular Longevity, pp:11.

Mazza, G.; Kay, C. D.; Daayf, F. and Lattanzio, V. (2008). Recent advances in polyphenols research. New York: Blackwell Publishing.

Mehta, G.; Nayak, U. R. and Dev, S. (1966). Bakuchiol, a novel monoterpenoid. Tetrahedron Letters, 7(38):4561-4567.

Miao, L.; Yun, X.; Tao, R.; Wang, Y.; Fan, G.; Zhu, Y.; Cai, T.; Zhu, Z.; Yan, C. and Gao, X. (2018). Bakuchiol exhibits antimetastasis activity through NF-κB cross-talk signaling with AR and ERβ in androgen-independent prostate cancer cells PC-3. Journal of Pharmacological Sciences, 138(1):1-8.

Miller, V. M. and Duckles, S. P. (2008). Vascular actions of estrogens: Functional implications. Pharmacological Reviews, 60(2):210-241.

Mohd Sahardi, N. F. N. and Makpol, S. (2019). Ginger (*Zingiber officinale* Roscoe) in the prevention of ageing and degenerative diseases: Review of current evidence. Evidence-Based Complementary and Alternative Medicine, 2019. https://www.hindawi.com/journals/ecam/2019/5054395/

Mohri-Shiomi, A. and Garsin, D. A. (2008). Insulin signaling and the heat shock response modulate protein homeostasis in the *Caenorhabditis elegans* intestine during infection. Journal of Biological Chemistry, 283(1):194-201.

Murphy, C. T. and Hu, P. J. (2018). Insulin/insulin-like growth factor signaling in *C. elegans*. WormBook: The Online Review of *C. elegans* Biology. https://www.ncbi.nlm.nih.gov/books/NBK179230/

Nizam, N. N.; Mahmud, S.; Kamruzzaman, M. and Hasan, M. K. (2023). Bakuchiol and its pharmacological benefits. F1000Research, 12:29.

Onken, B. and Driscoll, M. (2010). Metformin induces a dietary restriction-like state and the oxidative stress response to extend *C. elegans* healthspan *via* AMPK, LKB1 and SKN-1. PloS One, 5(1):8758.

Pandey, S. and Chauhan, P. S. (2021). Role of phytomolecules on the basic biology of ageing. Evidence Based Validation of Traditional Medicines: A comprehensive Approach, pp:129-139.

Pant, A.; Saikia, S. K.; Shukla, V.; Asthana, J.; Akhoon, B. A. and Pandey, R. (2014). Beta-caryophyllene modulates expression of stress response genes and mediates longevity in *Caenorhabditis elegans*. Experimental Gerontology, 57:81-95.

Prahlad, V.; Cornelius, T. and Morimoto, R. I. (2008). Regulation of the cellular heat shock response in *Caenorhabditis elegans* by thermo sensory neurons. Science, 320(5877):811-814.

Puyana, C.; Chandan, N. and Tsoukas, M. (2022). Applications of bakuchiol in dermatology: Systematic review of the literature. Journal of Cosmetic Dermatology, **21**(12):6636-6643.

Ranjan, S.; Trivedi, S.; Sharma, S.; Khan, S. and Pandey, R. (2023). Bakuchiol modulates acetylcholine synthesis and alleviates Aβ proteotoxicity. Natural Product Research, pp:1-5.

Rantakokko, M.; Mänty, M. and Rantanen, T. (2013). Mobility decline in old age. Exercise and Sport Sciences Reviews, **41**(1):19-25.

Riddle, D. L.; Blumenthal, T.; Meyer, B. J. and Priess, J. R. (1997). *C. elegans* ii.

Rodriguez, M.; Snoek, L. B.; De Bono, M. and Kammenga, J. E. (2013). Worms under stress: *C. elegans* stress response and its relevance to complex human disease and ageing. Trends in Genetics, **29**(6):367-374.

Sadgrove, N. J.; Oblong, J. E. and Simmonds, M. S. J. (2021). Inspired by vitamin A for anti ageing: Searching for plant derived functional retinoid analogues. Skin Health and Disease, **1**(3):36.

Salminen, A. and Kaarniranta, K. (2012). AMP-activated protein kinase (AMPK) controls the ageing process *via* an integrated signaling network. Ageing Research Reviews, **11**(2):230-241.

Sen, P.; Shah, P. P.; Nativio, R. and Berger, S. L. (2016). Epigenetic mechanisms of longevity and ageing. Cell, **166**(4):822-839.

Senchuk, M. M.; Dues, D. J. and Van Raamsdonk, J. M. (2017). Measuring oxidative stress in *Caenorhabditis elegans*: Paraquat and juglone sensitivity assays. Bio. Protocol., **7**(1):2086-2086.

Sharma, S.; Kochhar, K. P.; Jayasundar R. and Divya R. M. (2021). Therapeutic potential of Indian traditional medicines in Parkinson's disease. Ann. Phytomed., **10**(2):252-263.

Shukla, P.; Pant, A. and Pandey, R. (2019). Limonene attenuates oxidative stress and extends longevity in *Caenorhabditis elegans*. Current Science, **116**(6):959-965.

Shukla, V.; Yadav, D.; Phulara, S. C.; Gupta, M. M.; Saikia, S. K. and Pandey, R. (2012). Longevity-promoting effects of 4-hydroxy-E-globularinin in *Caenorhabditis elegans*. Free Radical Biology and Medicine, **53**(10):1848-1856.

Siddiqui, T.; Gupta, K.; Sharma, V.; Kumar, S.; Raj, G. and Shahu, A. (2023). Exploring the holistic potential of medicinal plants for improving human health. Ann. Phytomed., **12**(2):360-372.

Sies, H. (1993). Strategies of antioxidant defense. European Journal of Biochemistry, **215**(2):213-219.

Singh, A.; Kukreti, R.; Saso, L. and Kukreti, S. (2019). Oxidative stress: A key modulator in neurodegenerative diseases. Molecules, **24**(8):1583.

Tang, X.; Guo, X.; Geng, D. and Weng, L. J. (2019). D-Limonene protects PC12 cells against corticosterone induced neurotoxicity by activating the AMPK pathway. Environmental Toxicology and Pharmacology, **70**:103192.

Tatar, M.; Bartke, A. and Antebi, A. (2003). The endocrine regulation of ageing by insulin-like signals. Science, **299**(5611):1346-1351. https://doi.org/10.1126/science.1081447

Tullet, J. M. A.; Green, J. W.; Au, C.;Benedetto, A.; Thompson, M. A.; Clark, E.; Gilliat, A. F.; Young, A.; Schmeisser, K. and Gems, D. (2017). The SKN 1/Nrf2 transcription factor can protect against oxidative stress and increase lifespan in *C. elegans* by distinct mechanisms. Ageing Cell, **16**(5):1191-1194.

Uno, M. and Nishida, E. (2016). Lifespan-regulating genes in *C. elegans*. NPJ Ageing and Mechanisms of Disease, **2**(1):1-8.

Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M. T.; Mazur, M. and Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry and Cell Biology, **39**(1):44-84.

Vellai, T.; Takacs-Vellai, K.; Zhang, Y.; Kovacs, A. L.; Orosz, L. and Müller, F. (2003). Influence of TOR kinase on lifespan in *C. elegans*. Nature, **426**(6967):620-620.

Villa, A.; Vegeto, E.; Poletti, A. and Maggi, A. (2016). Estrogens, neuroinflammation and neurodegeneration. Endocrine Reviews, **37**(4):372-402.

Wang, J.; Li, W.; Yu, S.; Xie, H. and Han, H. (2014). Catalpol regulates function of hypothalamic-pituitary adrenocortical axis in an Alzheimer's disease rat model. Die Pharmazie-An International Journal of Pharmaceutical Sciences, **69**(9):688-693.

Wang, Y.; He, J.; Liao, M.; Hu, M.; Li, W.; Ouyang, H.; Wang, X.; Ye, T.; Zhang, Y. and Ouyang, L. (2019). An overview of sirtuins as potential therapeutic target: Structure, function and modulators. European Journal of Medicinal Chemistry, **161**:48-77.

Wells, K. and Sands, M. (2022). Bakuchiol: More than just a retinol alternative.

Weng, Z. B.; Gao, Q. Q.; Wang, F.; Zhao, G. H.; Yin, F. Z.; Cai, B. C.; Chen, Z. P. and Li, W. D. (2015). Positive skeletal effect of two ingredients of *Psoralea corylifolia* L. on estrogen deficiency-induced osteoporosis and the possible mechanisms of action. Molecular and Cellular Endocrinology, **417**:103-113.

Wojtunik-Kulesza, K.; Rudkowska, M.; Kasprzak-Drozd, K.; Oniszczuk, A. and Borowicz-Reutt, K. (2021). Activity of selected group of monoterpenes in alzheimer's disease symptoms in experimental model studies-A non-systematic review. International Journal of Molecular Sciences, **22**(14):7366.

Wysocka, M. (2022). Bakuchiol-a plant-based retinol. The review article.

Wyss-Coray, T. (2016). Ageing, neurodegeneration and brain rejuvenation. Nature, **539**(7628):180-186.

Xin, Z.; Wu, X.; Ji, T.; Xu, B.; Han, Y.; Sun, M.; Jiang, S.; Li, T.; Hu, W. and Deng, C. (2019). Bakuchiol: A newly discovered warrior against organ damage. Pharmacological Research, **141**:208-213.

Xu, Y.; Gao, X.; Wang, L.; Yang, M. and Xie, R. (2021). Bakuchiol ameliorates cerebral ischemia reperfusion injury by modulating NLRP3 inflammasome and Nrf2 signaling. Respiratory Physiology and Neurobiology, **292**:103707.

Ye, X.; Linton, J. M.; Schork, N. J.; Buck, L. B. and Petrascheck, M. (2014). A pharmacological network for lifespan extension in *Caenorhabditis elegans*. Ageing Cell, **13**(2):206-215.

Yu, Q.; Zou, H.-M.; Wang, S.; Xu, Y.-M.; Li, J.-M. and Zhang, N. (2014). Regulative effect of bakuchiol on ESF-1 cells antiageing gene. Journal of Chinese Medicinal Materials, **37**(4):632-635.

Zhang, L.; Zhang, J.; Zhao, B. and Zhao-Wilson, X. (2012). Quinic Acid could be a potential rejuvenating natural compound by improving survival of *Caenorhabditis elegans* under deleterious conditions. Rejuvenation Research, **15**(6):573-583.

Zhang, W.; Xiao, D.; Mao, Q. and Xia, H. (2023). Role of neuroinflammation in neurodegeneration development. Signal Transduction and Targeted Therapy, **8**(1):267.

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