BAKUCHIOL: "THE PLANT-BASED POWERHOUSE FOR YOUTHFUL SKIN''

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ABSTRACT

A meroterpene phenol with promise anti-aging, anti-inflammatory, and antibacterial qualities, bakuchiol has attracted a lot of interest in the cosmetics business. This review paper offers a thorough analysis of bakuchiol's topical application, emphasizing its physicochemical characteristics, sources, bioactivities, nanotechnology delivery methods, and toxicological and regulatory issues. The main source of bakuchiol is the seeds of the Asian natural medicinal plant Psoralea corylifolia. But because of its poor seed germination rates and high seedling mortality, this plant is vulnerable. The review covers methods for reviving plants from fragments of roots as well as ways to confirm the legitimacy of the plant and stop fakes. Bakuchiol has antifungal, antibacterial, antioxidant, anti-inflammatory, antiaging, depigmenting, and anticancer properties that are the principal skin bioactivities. Bakuchiol is a promising substitute for topical retinoids because it has been demonstrated to have retinol-like effects on gene expression. Research conducted in vivo has indicated noteworthy decreases in photodamage, hyperpigmentation, wrinkles, and acne severity when bakuchiol is used either by itself or in conjunction with other products. The development of novel bakuchiol skin delivery methods, including micro- and nano-sized systems for medical and cosmetic uses, is also covered in the review. These delivery methods seek to strengthen bakuchiol's transdermal distribution and its physicochemical characteristics. Lastly, taking into account user safety as well as the influence on the environment, the paper discusses regulatory challenges, metabolic considerations, and toxicological concerns associated to the use of bakuchiol in cosmetic and dermo pharmaceutical formulations. As a result, readers will have a thorough understanding of the potential of bakuchiol as a natural retinol-like component in medicinal and cosmetic applications for skin health and youthfulness

Keyword: - *Bakuchiol, plant-based skincare, Anti-aging, Psoralea corylifolia, Meroterpene, Antioxidant.*

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1. INTRODUCTION

A naturally occurring substance called bakuchiol exists in the seeds and leaves of the Psoralea corylifolia plant, consequently referred as babchi. Bakuchiol, traditionally utilized in Chinese and Ayurvedic medicine, has drawn a lot concerning interest recently as a possible skincare substitute for retinoids, especially retinol. In contrast to retinol, which is an artificially produced form of vitamin A, bakuchiol is a non-sensitizing substance derived from plants. Despite having a very different structure from retinoids, it has comparable effects on the skin. It has been demonstrated that bakuchiol possesses anti-aging properties through inducing the creation of collagen, diminishing the visibility of fine lines and wrinkles, and enhancing skin elasticity. [1,2] Its antibacterial, anti-inflammatory, and antioxidant qualities also make it a good choice for treating acne and other skin issues. Bakuchiol's improved tolerability over conventional retinoids is one of its main benefits. Retinoids have a number of negative effects that can limit its use, especially for people with sensitive skin, including as dryness, inflammation, and photosensitivity. [3,4] For people who cannot take retinoids, bakuchiol is a desirable alternative because it is generally well-tolerated and has fewer documented side effects. As a novel, plant-based substitute for retinoids, bakuchiol provides better tolerability along with comparable skin benefits. As it becomes more and more well-known in the skincare sector, more research is necessary to properly comprehend its modes of action, effectiveness, and potential as a commonplace ingredient in skincare products. [2,4,5]

Background history of Bakuchiol: Mehta et al. isolated this meroterpenoid for the first time in 1966 from the seeds of Psoralea corylifolia, a plant used in traditional Chinese and Ayurvedic medicine. The Sanskrit word "Bakuchi," which refers to the plant, is the source of the name "Bakuchiol". The commercial use of bakuchiol, under the brand name Sytenol A, started in 2007, despite the fact that its complete synthesis was achieved in 1973. Due to its antibacterial, anti-inflammatory, and antioxidant qualities, it has drawn attention and shown promise in treating skin disorders and as a retinol substitute for anti-aging benefits. Clinical research has shown that, when compared to retinol, it is more effective in improving photoaging and enhancing skin tolerability. [4-6]

Psoralea corylifolia has long been used in traditional Chinese and Ayurvedic medicine: Bakuchiol, also known as Psoralea corylifolia, has a long history of traditional usage in Traditional Chinese Medicine (TCM) and Ayurveda. Ayurvedic medicine: Psoralea corylifolia is highly regarded in Ayurveda for its effectiveness in treating a variety of skin disorders, including vitiligo (leukoderma) and other skin ailments like psoriasis and eczema. The seeds are applied externally in a variety of forms, such as pastes and ointments. Their anti-inflammatory, aphrodisiac, and diuretic qualities are also used internally. Furthermore, the plant is used to treat conditions including asthma, fever, and digestive issues and is said to balance the doshas, especially Kapha and Vata. [5,6]

According to traditional Chinese medicine (TCM), Psoralea corylifolia is used to maintain the health of the kidneys and spleen and is seen as having a warm temperament. It is known for its antibacterial and anti-inflammatory qualities and is mostly used to treat skin conditions, including vitiligo. Additionally, the seeds are utilized to improve fertility and treat ailments including osteoporosis and nephritis. Because of its many therapeutic uses, Psoralea corylifolia has, in general, been a vital component of conventional medical procedures. Figure 1.1 gives structural illustration of bakuchiol [6-8]

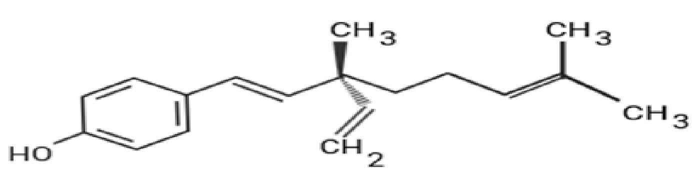


Fig 1.1: Structure of bakuchiol

1.1 Sources of Bakuchiol:

1.1.1 Natural Sources: The majority of bakuchiol comes from natural plant sources; Psoralea corylifolia is the most famous of these. The key bakuchiol sources and their importance are described in depth in the following sections: Botanical Description of Psoralea corylifolia, also known as the Babchi Plant:

A perennial herbaceous plant in the Fabaceae family is called Psoralea corylifolia. Asia's tropical and subtropical regions, which include Southeast Asia, China, and India, are home to it. Trifoliate leaves and tiny purple or white blooms adorn this normally 30- to 60-cm-tall plant.[4]

• Parts Used: The seeds and leaves of the babchi plant are the main sources of bakuchiol. Compared to other sections of the plant, the seeds have a larger concentration of bakuchiol.

• Traditional Use: Psoralea corylifolia has been utilized for its therapeutic qualities, including as treating skin diseases, rheumatism, and digestive disorders, in traditional Chinese and Ayurvedic medicine. Known as "Babchi," the seeds have played a significant role in various folk treatments.

• Extraction Techniques: A variety of techniques, such as solvent extraction, steam distillation, and supercritical fluid extraction, are used to extract bakuchiol from the seeds and leaves. High yields of bakuchiol are frequently achieved by solvent extraction using ethanol or methanol. [10]

1.1.2. Additional Plant Sources: Although Psoralea corylifolia is the main source, bakuchiol has also been found in other plants, albeit usually in smaller amounts:
• Psoralea glomerata (Babchi): It has also been discovered that Psoralea glomerata, a different species in the Psoralea genus, contains bakuchiol. Although it is not as widely used, this plant can provide bakuchiol in some areas.
• Psoralea leschenaultia: Although bakuchiol content in this plant, which grows in India and Southeast Asia, has been recorded, it is usually found at lesser concentrations than in Psoralea corylifolia.
Synthetic and Partial Synthetic Production: Advancements in synthetic and semi-synthetic bakuchiol production methods have coincided with growing interest in the compound, frequently with the goal of ensuring a steady supply and lowering expenses related to natural extraction.

• Chemical Synthesis: By creating synthetic pathways, chemists may now create bakuchiol from less complex chemical components. To create the bakuchiol structure, these techniques usually entail intricate organic procedures such as cyclization’s and oxidations.
• Benefits: By eliminating reliance on natural sources and lowering environmental effect, synthetic synthesis offers exact control over the purity and quantity of bakuchiol. [9]

Semisynthetic method:

• Microbial Fermentation: New research has looked into using genetically altered bacteria or yeast to ferment bakuchiol. By using metabolic engineering, bakuchiol can be biosynthesised from less complex substrates in this method.
• Plant Cell Cultures: Bakuchiol can also be made semi-synthetically by cultivating plant cells. It is not necessary to cultivate the whole plant on a big scale in order to create bakuchiol; these cell cultures can be kept under regulated conditions.

Industrial production: Commercial manufacturing of bakuchiol frequently blends natural extraction with synthetic and semi-synthetic interprets due to the increasing demand for the ingredient in pharmaceuticals and cosmetics. By using this strategy, the market's demands are met and a steady supply of superior bakuchiol is guaranteed. Table 1.1 gives classification of bakuchiol [4,10]

Table 1.1: Classification of Bakuchiol

Category	Scientific name
Kingdom	Plantae
Division	Magnoliophyte
Class	Magnoliopsida
Order	Fabales
Family	Fabaceae
Subfamily	Faboideae
Genus	Psoralea
Species	Psoralea

1.2 GEOGRAPHICAL DISTRIBUTION:

A plant-derived component called bakuchiol is widely used for dermatological products, mostly as a natural substitute for retinol. While it can be found in many different plants, Psoralea corylifolia, which is frequently referred to as babchi, is the primary source of it in terms of seeds and leaves. This is an in-depth examination of its geographic distribution:

- India: Native to a Indian subcontinent, Psoralea corylifolia is a widely distributed species there. It has long been employed in Unani and Ayurvedic medical treatment.
- China: The plant is originating to China as well, where it has long been utilized in traditional Chinese medicine.
- Southeast Asia: Malaysia, Vietnam, Thailand, and other different nations in Southeast Asia are home to Psoralea corylifolia.
- Africa: Although less widespread, the plant is present in various parts of Africa, notably Ethiopia.
- Other Regions: Psoralea corylifolia can be cultivated in various portions of the world with comparable climates, including certain tropical and Mediterranean regions, even though it appears most frequently in these places. The expansion of the plant is correlated with warm, tropical, and subtropical climates, as these are the conditions under which it usually grows.

1.3 COLLECTION AND CULTIVATION:

1.3.1 Seed Collection:

- Harvested Seeds: Both manual labour and a thresher are used to remove the seeds from the harvested plant material. The seeds undergo cleaning and drying in the shade to lower their moisture content after threshing. Extracting Bakuchiol, Preparation: The dried seeds are crushed to a coarse powder.
- Removing Solvents: Using a solvent such as ethanol, methanol, or hexane, bakuchiol is separated from the seed powder. For the bakuchiol to dissolve, the solvent is poured through the powdered seed.
- Purification: To get a crude extract, the extract is filtered and the solvent is evaporated at a lower pressure. To isolate pure bakuchiol, the crude extract is further refined utilizing methods such as column chromatography.
- 3.Quality Assurance: Testing: High-Performance Liquid Chromatography (HPLC) is used to test the finished product for bakuchiol concentration and purity. Storage: To avoid deterioration, bakuchiol should be kept out of the sun and heat in sealed containers. [11,12]

1.3.2 Cultivation of bakuchiol:

- Soil and Climate Requirements: Climate: Tropical and subtropical locations are ideal for Psoralea corylifolia growth. It needs a warm environment with lots of sunshine. 20°C to 35°C is the optimal temperature range.
  Soil: The plant loves sandy loam soil that drains well and has a pH of 6.5 to 7.5, which is slightly acidic to neutral. Although it may thrive in a variety of soil types, including saline and low soils, rich soils provide the highest yields. [13,14]
- Propagation: Seeds: The most often used means of propagation is by means of seeds. To improve germination, seeds should be steeped in warm water for 12 to 24 hours prior to planting. Sowing: At a depth of 1-2 cm, seeds are sown straight onto the field. Early monsoon season (June-July) is the ideal time to seed. Plant spacing: Plants should be arranged in rows, with a distance between each row of around 60 to 75 centimetres.
- Field Preparation:
  Preparation of Land: Deep plowing and leveling are necessary for the land. Compost or farmyard manure are examples of organic manure that should be added to the soil to increase fertility.
  Invasions: To avoid competition for nutrients, regular weeding is essential, especially in the early phases of development.
  Irrigation: Plants need to be watered moderately, especially in the early stages of development and flowering. Root rot can result from over-irrigation, hence it should be avoided.
- Fertilization:
  Fertilizers organic: Before sowing, it is recommended to apply well-decomposed organic manure. Fertilizers with chemicals (nitrogen, phosphorus, and potassium) fertilizers can be applied in a balanced manner; however, misuse should be avoided to protect the ecosystem.

- Control of Pests and Diseases: Typical Pests: Plants may be attacked by caterpillars and aphids. Pests can be managed with the help of organic insecticides, such as neem oil. Diseases: Powdery mildew and other fungal diseases can affect the plant. Air circulation and proper spacing contribute to a lower incidence of illness.
  Harvesting: When Should I Harvest? The plant takes 4-5 months to reach maturity. When the seeds get dark brown or black, harvesting is complete. Method: After cutting the entire plant closely to the ground, the seeds are harvested by threshing.[15]

2. BIOSYNTHESIS OF BAKUCHIOL:

Chart 2.1 illustrates the biosynthesis of Bakuchiol, a natural compound found in the Psoralea corylifolia plant. The process involves two distinct branches:[10]
1. Phenylpropanoid Pathway: This pathway originates from the amino acid Phenylalanine and leads to the formation of P-Coumaric acid.
2. Mevalonate Pathway: This pathway starts with Acetyl-CoA and Acetoacetyl-CoA and culminates in the formation of Geranyl pyrophosphate (GPP). [2,10]
Key Enzymes:
- Phenylalanine ammonia lyase
- Cinnamate 4-hydroxylase
- HMG-CoA reductase
- Mevalonate kinase

1. Precursor Molecules: The biosynthesis of bakuchiol starts with phenylalanine, an amino acid that serves as a precursor for many phenylpropanoids and terpenoids in plants
2. Formation of Cinnamic Acid: Phenylalanine undergoes deamination (removal of an amino group) by the enzyme phenylalanine ammonia-lyase (PAL), forming cinnamic acid.
3. Coumarin Pathway: Cinnamic acid is hydroxylated by cinnamate 4-hydroxylase (C4H) to form p-coumaric acid. P-coumaric acid is further hydroxylated to form 4-hydroxycinnamic acid, which is a key intermediate in the biosynthesis of many coumarins.
4. Formation of the Prenylated Phenol: The pathway involves the prenylation (attachment of a prenyl group) of a phenolic compound. The prenylation is likely catalyzed by a prenyltransferase enzyme, leading to the formation of a prenylated intermediate.
5. Cyclization and Reduction: The prenylated intermediate undergoes cyclization and reduction reactions to form bakuchiol. These reactions are mediated by enzymes specific to the plant’s metabolic pathways, leading to the final bakuchiol structure, which is a monoterpene phenol.
6. Final Product: The result of these reactions is bakuchiol, which is a meroterpene, combining features of both phenolic and terpenoid structures.

This biosynthetic pathway is part of the plant's secondary metabolism, which produces compounds that help in defense against herbivores, pathogens, and environmental stresses. The exact enzymes and steps can vary between species and environmental conditions. [16,17]

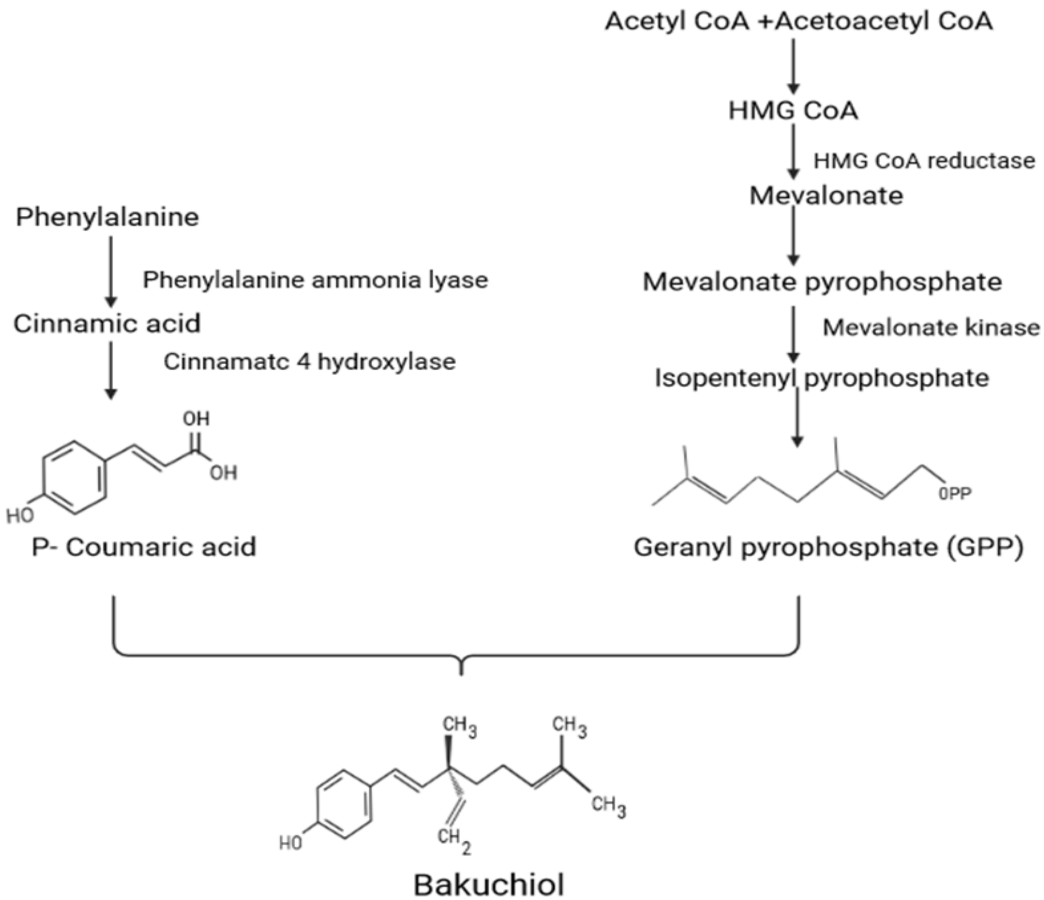


Chart 2.1 Bio-synthesis of bakuchiol

3. MECHANISM OF BAKUCHIOL:

3.1 Anti-Neuroinflammatory Effect :

Fig 3.1 illustrates the anti-neuroinflammatory effects of Bakuchiol, a compound found in the plant Psoralea corylifolia. It focuses on how Bakuchiol interacts with a specific signaling pathway in microglia cells, which are immune cells in the brain. [4,18]

• Key Components:

Cell Membrane: This is the outer boundary of the BV-2 microglia cell.

LPS (Lipopolysaccharide): A molecule that triggers inflammation and is often used in research to study inflammatory responses.

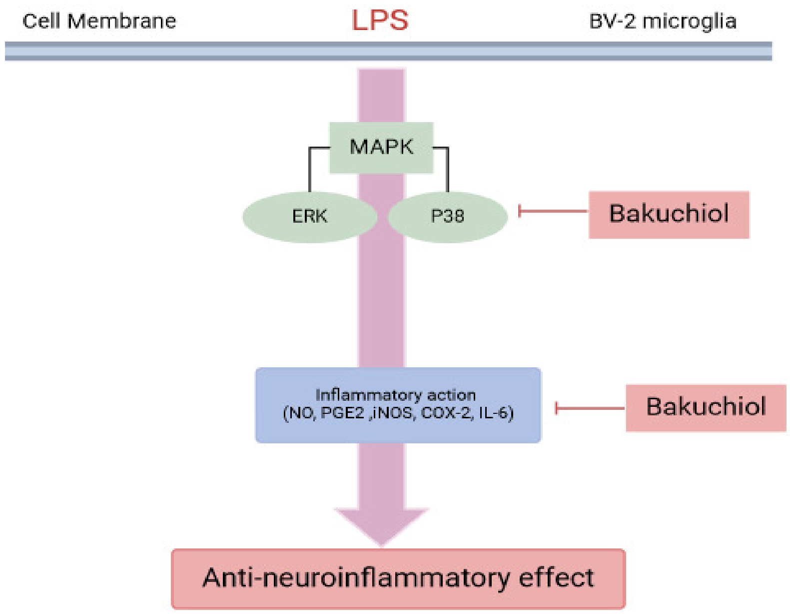


Fig.3.1 Mechanism of Bakuchiol

BV-2 microglia: A type of microglia cell commonly used in research.

MAPK (Mitogen-Activated Protein Kinase): A family of proteins involved in various cellular processes, including inflammation.

ERK and P38: Two specific types of MAPK proteins.

Bakuchiol: The compound of interest, shown to inhibit the activity of P38.

Inflammatory action: Processes that promote inflammation, including the production of molecules like NO, PGE2, INOS, COX-2, and IL-6.

1. LPS Stimulation: The pathway is initiated by the exposure of BV-2 microglia cells to Lipopolysaccharide (LPS), a component of bacterial cell walls that triggers an inflammatory response.
2. MAPK Activation: LPS binds to receptors on the cell membrane, leading to the activation of Mitogen-Activated Protein Kinases (MAPKs).
3. ERK and P38 Activation: MAPK activation results in the phosphorylation and activation of two key downstream kinases: Extracellular Signal-Regulated Kinase (ERK) and p38.
4. Inflammatory Response: Activated ERK and P38 induce the production of various inflammatory mediators, including Nitric Oxide (NO), Prostaglandin E2 (PGE2), Inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2), and Interleukin-6 (IL-6).
5. Bakuchiol Intervention: The image indicates that Bakuchiol inhibits the activation of both ERK and P38, effectively blocking the inflammatory response.
6. Anti-Neuroinflammatory Effect**:** By suppressing the production of inflammatory mediators, Bakuchiol exerts an anti-neuroinflammatory effect, potentially protecting neurons from damage. [19,20]

Anti-neuroinflammatory effect: The overall outcome of Bakuchiol's action, reducing inflammation in the brain.

3.2 Antimicrobial Mechanism:

Bakuchiol's capacity to prevent the growth of certain bacteria, such as Streptococcus mutans, a major cause of dental cavities, is the main way that it demonstrates its antimicrobial qualities.

Its antibacterial action consists of: Bactericidal Effects: Bakuchiol significantly inhibits the development and adhesion of bacteria, exhibiting bactericidal action against both Gram-positive and Gram-negative bacteria.

Preventing the Formation of Biofilms: This action impedes the growth of bacterial colonies known as biofilms, which can become more resistant to therapy. Stability in Temperature and pH: Bakuchiol is adaptable to a wide range of conditions and retains its antibacterial effectiveness in a variety of pH values.

By efficiently addressing microbial infections, these mechanisms support its possible application in skincare and oral care formulations. [5,20]

3.3 Antioxidant Mechanism:

The antioxidant mechanism of bakuchiol involves several intricate processes and pathways that help neutralize oxidative stress and protect cells from damage. Here's a detailed overview of its antioxidant mechanisms: [21,22]

1.Scavenging of Reactive Oxygen Species (ROS): Direct Radical Scavenging: Bakuchiol directly neutralizes various types of ROS, including superoxide anions (O_2^-), hydroxyl radicals (OH•), and hydrogen peroxide (H_2O_2). By scavenging these reactive species, bakuchiol prevents them from causing oxidative damage to cellular components such as lipids, proteins, and DNA. [23,24]

2. Modulation of Antioxidant Enzyme Activity: Enhancement of Endogenous Antioxidant Enzymes: Bakuchiol induces the activity of key endogenous antioxidant enzymes, such as: Superoxide Dismutase (SOD): Catalyzes the conversion of superoxide radicals into hydrogen peroxide and oxygen, reducing oxidative stress. Catalase: Decomposes hydrogen peroxide into water and oxygen, mitigating potential oxidative damage. Glutathione Peroxidase (GPx): Reduces hydrogen peroxide and lipid peroxides, playing a critical role in cellular antioxidant defense. Regulation of Antioxidant Gene Expression: Bakuchiol activates transcription factors like Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), which upregulates the expression of genes encoding antioxidant enzymes and other protective proteins. [25-27]

3. Inhibition of Lipid Peroxidation: Prevention of Lipid Peroxide Formation: Bakuchiol inhibits the oxidation of lipids in cell membranes, a process known as lipid peroxidation. By preventing lipid peroxidation, bakuchiol protects cell membranes from damage and maintains cellular integrity.

4. Protection of Cellular Macromolecules: DNA Protection: By reducing oxidative stress, bakuchiol helps protect DNA from oxidative damage, which can lead to mutations and contribute to aging and cancer. Protein Protection: Bakuchiol prevents oxidative modifications of proteins, including the formation of protein carbonyls and advanced glycation end-products (AGEs), which are associated with cellular dysfunction and aging. [24,26]

5. Reduction of Oxidative Stress-Induced Inflammation: Interference with Inflammatory Pathways: Bakuchiol reduces oxidative stress-induced inflammation by inhibiting pathways that lead to the production of inflammatory cytokines. This effect is partly mediated by its antioxidant properties, which limit the activation of inflammatory signaling cascades.

6. Stabilization of Cellular Redox Status: Maintenance of Redox Homeostasis: Bakuchiol contributes to the maintenance of a balanced cellular redox state by modulating the levels of oxidants and antioxidants. This balance is crucial for preventing oxidative stress and ensuring proper cellular function. [28-30]

7. Synergistic Effects with Other Antioxidants: Complementary Antioxidant Action: Bakuchiol may work synergistically with other antioxidants present in the skin or diet, enhancing the overall antioxidant capacity and providing more comprehensive protection against oxidative damage. [30,31]

3.4 Anti-cancer Mechanism:

1. Induction of Apoptosis: Bakuchiol has been shown to induce apoptosis (programmed cell death) in various cancer cell lines. This involves activation of caspases, disruption of mitochondrial membrane potential, and release of cytochrome c. Studies have indicated that Bakuchiol can upregulate pro-apoptotic proteins like Bax and downregulate anti-apoptotic proteins like Bcl-2. [32-35]

2. Cell Cycle Arrest: Bakuchiol can halt the cell cycle at specific phases, preventing cancer cells from dividing and proliferating. It has been observed to induce cell cycle arrest at the G1 and S phases. This effect is associated with the regulation of cyclin-dependent kinases (CDKs) and their inhibitors. [36,37]

3. Inhibition of Angiogenesis: Bakuchiol may suppress the formation of new blood vessels (angiogenesis), which is essential for tumor growth and metastasis. This effect is likely mediated through the inhibition of vascular endothelial growth factor (VEGF) and other angiogenic factors.[38]
4. Anti-Inflammatory Effects: Chronic inflammation is linked to cancer development. Bakuchiol's anti-inflammatory properties can contribute to its anti-cancer effects by reducing inflammation and oxidative stress. This involves inhibition of inflammatory mediators like cytokines and chemokines. [38-42]
5. Modulation of Signaling Pathways: Bakuchiol has been shown to interfere with various signaling pathways involved in cancer cell growth and survival, such as the PI3K/AKT, MAPK, and NF-κB pathways. By inhibiting these pathways, Bakuchiol can suppress cancer cell proliferation and promote apoptosis. [42-46]
6. Targeting Cancer Stem Cells: Cancer stem cells are responsible for tumor initiation and recurrence. Bakuchiol has demonstrated the potential to target these cells by inhibiting their self-renewal capacity and inducing apoptosis. [46-50]

3.5 Anti-inflammatory Mechanism:

Bakuchiol's anti-inflammatory effects are mediated through several intricate biochemical mechanisms that reduce inflammation and mitigate related cellular damage. Here's a detailed overview of how bakuchiol exerts its anti-inflammatory actions: [26,50,51]

1. Inhibition of Pro-inflammatory Cytokines: Reduction of Cytokine Production: Bakuchiol inhibits the production of key pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). This action is crucial in reducing the inflammatory response and subsequent tissue damage. Regulation of Cytokine Signaling: By modulating the signaling pathways that lead to cytokine production, bakuchiol helps in maintaining a balanced immune response. [52-55]
2. Modulation of Nuclear Factor-kappa B (NF-κB) Pathway: Inhibition of NF-κB Activation: NF-κB is a transcription factor that, when activated, triggers the expression of various pro-inflammatory genes. Bakuchiol inhibits the activation of NF-κB, thus preventing the transcription of genes involved in inflammation. Preventing IκB Degradation: NF-κB is typically kept in the cytoplasm in an inactive form bound to IκB proteins. Bakuchiol may prevent the degradation of IκB, thereby keeping NF-κB sequestered and inactive. [56-58]
3. Reduction of Oxidative Stress: Scavenging Reactive Oxygen Species (ROS): By scavenging ROS, bakuchiol reduces oxidative stress, which is a significant contributor to inflammation. High levels of ROS can activate various inflammatory pathways, so their reduction helps in mitigating inflammation. Preservation of Antioxidant Defenses: Bakuchiol helps maintain the activity of cellular antioxidant enzymes, which further decreases oxidative stress and prevents inflammatory damage.[59]
4. Inhibition of Inflammatory Enzymes: Cyclooxygenase (COX) Inhibition: Bakuchiol inhibits COX enzymes, particularly COX-2, which are involved in the production of prostaglandins that promote inflammation and pain. This inhibition helps reduce inflammatory responses. Lipoxygenase (LOX) Pathway Modulation: Bakuchiol affects the LOX pathway, which is involved in the synthesis of leukotrienes, another group of inflammatory mediators. By modulating this pathway, bakuchiol reduces the inflammatory response.59,60,61]
5. Impact on Immune Cell Function: Modulation of Macrophage Polarization: Bakuchiol influences the polarization of macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. This shift helps in resolving inflammation and promoting tissue repair. Inhibition of Leukocyte Activation: Bakuchiol can modulate the activation and migration of leukocytes (white blood cells) involved in inflammatory responses, thereby reducing inflammation and tissue damage.
6. Regulation of Inflammatory Pathways: Mitogen-Activated Protein Kinases (MAPKs) Pathway: Bakuchiol inhibits the MAPK pathway, which includes ERK, JNK, and p38 MAPKs. These pathways are crucial for the activation of inflammatory transcription factors and the production of inflammatory cytokines. Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) Pathway: Bakuchiol may also affect the JAK/STAT signaling pathway, which is involved in the transcription of pro-inflammatory genes.
7. Enhancement of Skin Barrier Function: Strengthening the Skin Barrier: Bakuchiol improves the skin barrier function, which helps in reducing inflammation triggered by external irritants and pathogens. A stronger skin barrier minimizes inflammatory responses and supports overall skin health. [62,63]

4. EXTRACTION METHODS:

4.1 Solvent Extraction:

Bakuchiol from Psoralea corylifolia is commonly isolated via solvent extraction. The procedure is outlined in full below: [64,65]

1.Plant Material Preparation Extraction: Gather the mature leaves or seeds of Psoralea corylifolia that have a high level of bakuchiol.

Drying: By removing moisture from the plant material, drying promotes extraction efficiency and helps stop bakuchiol from degrading. For the solvent to work upon as much surface area as possible, grind or crush the dry plant material into a coarse powder. Grinding: To increase the surface area that the solvent may operate upon, crush or grind the dried plant material into a coarse powder.

2.Selection of Solvent Typically solvents include acetone, methanol, ethanol, and hexane. The extraction's accuracy and selectivity may be impacted by the solvent selection.
properties of a solvent: The best solvent to use is one that can dissolve bakuchiol with the least amount of unwanted chemicals being extracted.

3.Extracting Method Maceration involves soaking the powdered plant in the selected solvent. Typically, the plant material to solvent ratio falls between 1:5 and 1:10. Let it sit for a while (around 24 to 48 hours), stirring it now and again to improve extraction.
Filtration: To get rid of solid plant remains, filter the mixture after maceration. A vacuum filtration system, filter paper, or a sieve can be used for this.
Re-extraction (Optional): To guarantee the highest yield, the extraction process may occasionally be carried out again using a new solvent. Sequential extraction is the term for this procedure.

4.Extracting Solvents Utilizing evaporation procedures, extract the solvent from the filtrate. Two popular techniques are simple evaporation in a fume hood or rotating evaporation, which lowers the solvent under low pressure. The bakuchiol is isolated by concentration of the solvent-free extract. Any residues of solvent may be eliminated by processing this further.

5. Analysis and Purification: If required, use further techniques such as chromatography (e.g., column chromatography) to separate bakuchiol from other components in order to purify the extract.
Analysis: To determine the purity and concentration of bakuchiol in the final extract, use analytical methods such as high-performance liquid chromatography (HPLC).
6.Conditions for Storage: To stop deterioration, keep the finished bakuchiol extract in a cold, dark area. The stability and effectiveness of the chemical are preserved under ideal storage conditions. [66-69]

4.2 Steam Distillation:

1. Plant Material Preparation
When there is a high concentration of bakuchiol in the plant parts (leaves or seeds), harvest them. Cleaning: Give the plant material a quick rinse to get rid of any debris or pollutants. The plant material can be chopped or ground to expand its surface area, which improves the extraction efficiency. [70,71]

Steam Distillation Equipment Setup

Distillation Unit: A steam generator, a receiving flask, a condenser, and a distillation flask are usually included in the setup.

Steam Generator: Generates steam that is used to flow through the plant material.

Distillation Flask: This vessel holds the plant material and let’s steam flow through.

Condenser: Cools and condenses the vapours of essential oils and steam into a liquid.

Receiving Flash: Gathers the condensed liquid, which has water and essential oil in it.

Steam Distillation Procedure

Loading Fill the distillation flask with the prepared plant material.

Steam Generation: To make steam, heat the water in the steam generator.

Steam Passage: Pass the steam through the plant material in the flask used for distillation. Volatile substances, such as bakuchiol, are carried by the steam.

Condensation: The volatile chemicals and steam are sent into the condenser, where the steam cools and condenses back into liquid form.

Separation: The condensed liquid is gathered in the receiving flask, containing water and the essential oil.

Bakuchiol separation

2.Decantation: Let the liquid in the receiving flask to partition into two layers: essential oil and water (hydrosol). The layer of essential oils will contain bakuchiol. Using a separating funnel or decantation, carefully extract the essential oil from the aqueous layer.

3.Purification and Concentration

Purification: If required, use methods like fractional distillation or chromatography to further purify the essential oil in order to separate bakuchiol.

Concentration: If necessary, concentrate the essential oil to increase the bakuchiol concentration.

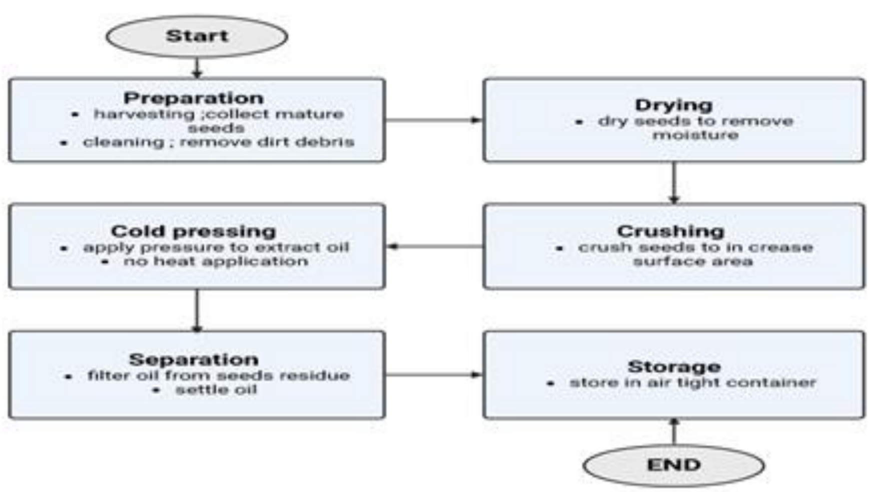
4.Examining and Keeping

Analytical techniques like gas chromatography (GC) can be used to ascertain the amount and purity of bakuchiol present in the essential oil.

5.Storage: To keep it from degrading, keep the purified bakuchiol cold and dark. To preserve the stability of the oil, use airtight containers.[72]

4.3 Cold Pressing:

Utilizing a mechanical process called cold pressing, oils are mechanically extracted from plant materials—usually seeds or fruits—without the use of heat. The following crucial procedures would be involved in the extraction of bakuchiol, is given in the flow chart 4.1



Flow Chart 4.1 Cold Pressing Method of Extraction

1.Preparation
Harvesting: Gather Psoralea corylifolia plant ripe seeds.
Cleaning: Give the seeds a good cleaning to get rid of any dirt, debris, or contaminants.
2. Drying: To lower the moisture content of the seeds and enhance oil extraction while preventing spoiling, drying is frequently used. To prevent too much heat, this can be done in a controlled setting.
3. Crushing: To break the dry seeds into smaller bits, they are mechanically crushed or ground. This expands the oil extraction surface area.
4. Cold Pressing:
Pressing: The crushed seeds are put into a cold press, which applies pressure using a mechanical or hydraulic press. By applying pressure, the oil is extracted from the seeds while the temperature remains low.
No Heat: Applying heat is not done during the cold pressing process, which is its primary characteristic. This stops oxidation and aids in maintaining the integrity of delicate substances like bakuchiol.
5.Separation:
Filtration: Following pressing, the oil and solid seed residue combination is filtered. In this stage, the extracted oil is separated from the leftover seed cake. Allowing the oil to settle for a while can help get rid of any last bits of small particles.
6. Storage: To keep the extracted oil from deteriorating, it is kept in sealed containers in a cold, dark environment. Maintaining the effectiveness and purity of the bakuchiol requires proper storage.
Since heat would normally break down delicate molecules, cold pressing maintains the extracted oil's inherent qualities, including bakuchiol. For the extraction of premium natural oil, this approach is frequently chosen.[73,74]

4.4 Supercritical fluid Extraction:

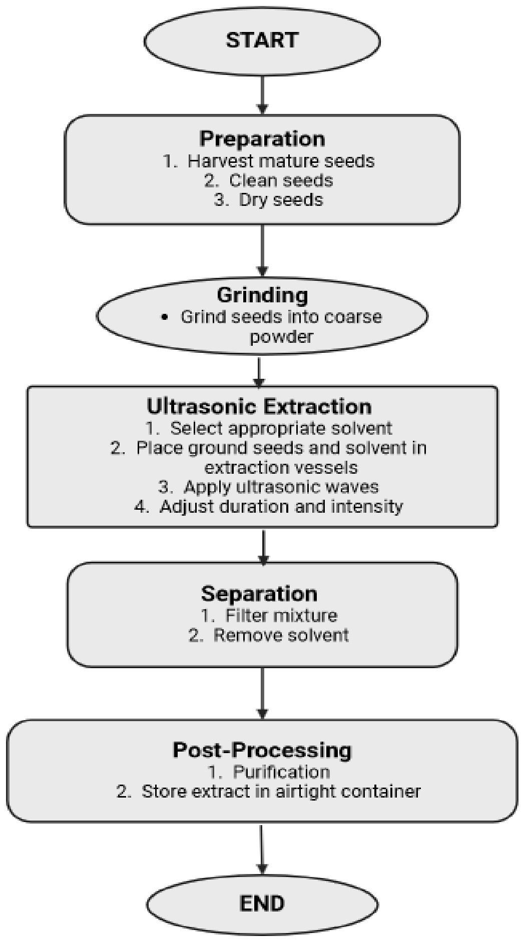
1. Preparation: Harvesting: Gather the ripe seeds of Psoralea corylifolia, the plant that yields bakuchiol.
Cleaning and Drying: To get rid of impurities and lower the moisture level, clean and dry the seeds. In order to prevent problems during extraction, this is crucial.
2. Crushing: To enhance the surface area that the supercritical fluid may interact with, crush the dried seeds into a coarse powder. Extractive efficiency is increased as a result. [84,85]
3. Setup for Supercritical Fluid Extraction:
Supercritical Liquid: The most often utilized fluid is supercritical CO2. Because CO2 possesses characteristics of both a gas and a liquid in its supercritical form, it may efficiently permeate through solids and dissolve molecules.
Extraction Chamber: The supercritical fluid is introduced to the powdered material once it is placed into the extraction chamber. [86,87]
4.Extraction Process:
Pressurization: In order to get the CO2 to its supercritical condition, pressure is used. Generally, 31.1°C (88°F) to 70°C (158°F) of temperature and pressure are needed for supercritical CO_2.
Material Flow: The supercritical CO_2 is then sent through the extraction chamber that holds the ground seeds powder. Bakuchiol and other compounds can be dissolved from the plant material due to the strong solvating power of CO_2 in this condition.
Controlling the solvating power of CO2 can facilitate the selective extraction of bakuchiol while reducing the extraction of undesirable compounds. This is achieved by varying the temperature and pressure.
5. Separating:
Collection: Once the dissolved bakuchiol is added to the CO_2, it leaves the extraction chamber and is sent to a separation vessel.
Decompression: The pressure in the separation vessel is lowered, allowing the CO2 to return to its gaseous form. Bakuchiol precipitates out when CO_2 runs out of solvating power.
Filtration: The bakuchiol is collected and, if required, might undergo further purification.
6.Post-Processing: Recycling CO2: This step makes the process more sustainable because CO2 may be recovered and utilized again in later extraction procedures.
Purification: To further isolate and purify bakuchiol, more purification procedures like chromatography may be used as needed. [84,92]
7.Storage: Finished Product: To preserve its stability and efficacy, the extracted bakuchiol is kept in sealed containers away from heat and light. [89-92]

Benefits of Fluid Extraction Under Supercritical Conditions:

1.High-purity extraction of certain chemicals is made possible via selective extraction.
2. No Solvent Residues: Because CO2 leaves no residue, it is the perfect choice for situations where purity is essential.
3. Eco-Friendly: CO2 is recyclable and a somewhat safe solvent. [85,86]

4.5 Ultrasonic Extraction:

The process known as "ultrasonic extraction" makes use of ultrasonic waves to improve the extraction of chemicals from plant materials. This technique works very well for removing substances from Psoralea corylifolia seeds, such as bakuchiol. An extensive rundown of the ultrasonic extraction procedure is provided below in flow chart 4.2: [73,74]



Flow chart 4.2 Ultrasonic Extraction Method

1. Preparation Harvesting: Gather Psoralea corylifolia's fully developed seeds.
Washing: To get rid of any impurities and dirt, wash the seeds. Reducing the moisture level of the seeds by drying aids in improved extraction and inhibits the development of microorganisms.
2. Grinding
Pulverize the desiccated seeds until they form a rough paste. This boosts extraction process efficiency by increasing surface area.
3. The Ultrasonic Extraction Setup
Picking a Solvent: Pick a suitable solvent that has the ability to dissolve bakuchiol. Ethanol, methanol, and/or a combination of solvents are typical solvents.
Extraction Vessel: Fill an extraction vessel that can withstand ultrasonic treatment with the powdered seeds and solvent.

4. Process of Ultrasonic Extraction Sonic Waves: Using high-frequency sound waves (usually between 20 kHz and 1 MHz), ultrasonic extraction produces cavitation in the solvent. The development and disintegration of tiny bubbles inside the liquid is referred to as cavitation.
Effect of Cavitation: Shock waves and microturbulences generated by the severe pressure fluctuations brought on by cavitation intensify the rupture of plant cell walls and facilitate the release of bakuchiol into the solvent. Processing: A probe or bath that uses ultrasonic waves is used to expose the extraction vessel to these vibrations. The material and intended yield determine how long and how hard the ultrasonic treatment should be applied. [75-77]
5.Separation Filtration: Following the ultrasonic extraction process, strain the mixture to extract the bakuchiol-containing liquid extract and discard the solid materials.
Removal of Solvent: If required, use methods such as rotary evaporation to remove the solvent. By doing this, the extract is concentrated and the bakuchiol is separated.
6. Post-Processing Purification: If more purification is required, other techniques such liquid-liquid extraction or chromatography may be used to further isolate and purify bakuchiol.
Storage: To preserve the final bakuchiol extract's efficacy and stability, keep it in sealed containers in a cold, dark area. [78-80]

Benefits of Ultrasonic Extraction Efficiency:
1.Better than traditional techniques in terms of extraction yield and speed.
2.Selective extraction: It is possible to maximize the extraction of desired molecules and minimize the extraction of undesirable ones.
3.Decreased Solvent Use: Effective extraction may be accomplished with a smaller amount of solvent, which is better for the environment. [80-83]

All things considered, ultrasonic extraction is an effective approach that improves the selectivity and efficiency of extracting chemicals from plant materials, such as bakuchiol. As such, it is useful for both research and industrial applications. [88,92]

5. COSMETIC USES OF BAKUCHIOL:

The cosmetics industry has taken a keen interest in bakuchiol, a plant-derived chemical, due to its possible advantages. It is said to be a milder substitute for retinol, providing comparable anti-aging and skin-improving benefits without the irritant side effects. Common cosmetic use is mention in figure 5.1 [93]

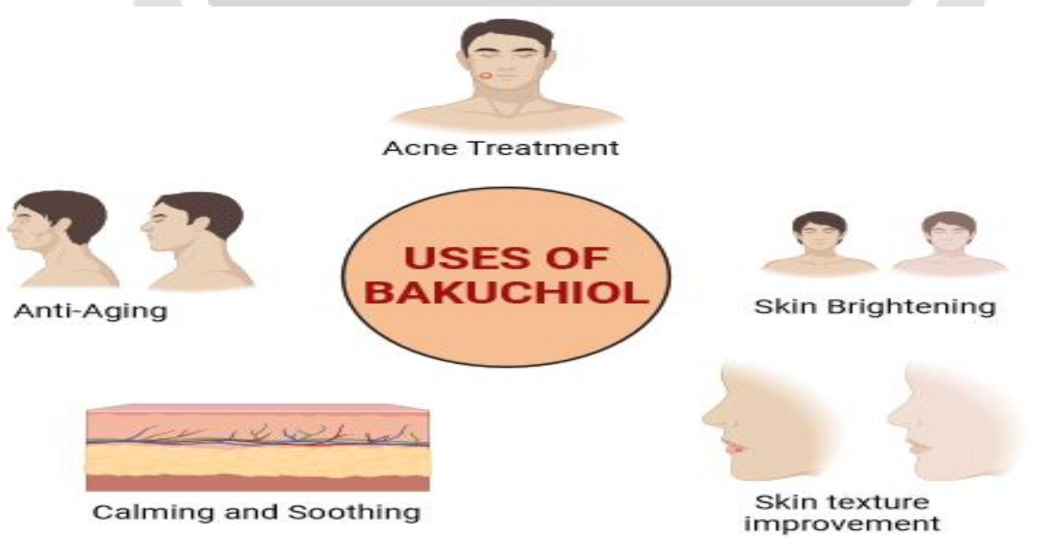


Fig.5.1 Uses of Bakuchiol for Cosmetic Purpose

5.1 Anti-aging Benefits:

1.Diminishes wrinkles and fine lines: Bakuchiol increases the synthesis of collagen, which enhances skin suppleness and minimizes the visibility of fine lines.
2.Improves skin texture: By encouraging cell turnover and exfoliation, it aids in the refinement of skin texture.
3.Evens out skin tone: Bakuchiol can aid skin tone by minimizing dark patches and hyperpigmentation. [94,95]

5.2 Acne Treatment:
1.Anti-inflammatory characteristics: The anti-inflammatory qualities of bakuchiol can aid in lowering acne-related redness and swelling.
2.Balances the production of sebum: By keeping sebum production in check, it can help avoid clogged pores and possible outbreaks. [96,97]

5.3 Skin Brightening:
1.Inhibits melanin production: Bakuchiol has the ability to lessen the synthesis of melanin, the pigment that causes uneven skin tone and dark patches on the skin.
2.Brightens complexion: Bakuchiol helps to brighten the skin by lowering hyperpigmentation and increasing skin clarity. [98,99]

5.4 Soothing and Calming:
1.Antioxidant qualities: Bakuchiol's antioxidant activity aids in shielding the skin from oxidative stress and environmental harm.
2.Minimizes sensitivity of the skin: It can calm inflamed skin and lessen redness.[100]

5.5 Other Potential Benefits:

1. Moisturizing: According to certain research, bakuchiol may have moisturizing qualities that enhance the skin's ability to hold moisture.
2.Sun protection: The antioxidant qualities of bakuchiol may provide some protection against UV ray damage, even though it is not a direct sunscreen. [100,101]

6. ADVERSE EFFECTS:

Bakuchiol is generally well-tolerated, but some side effects can occur, particularly with prolonged use. Common side effects are shown in figure 6.1 include: [69,102]

6.1 Skin Irritation: Mild irritation, scaling, or dermatitis may arise, especially in sensitive individuals.

6.2 Contact Dermatitis: Rarely reported but possible, often linked to other ingredients in formulations rather than bakuchiol itself

6.3 First Redness and Peeling: As a result of higher cell turnover, some consumers may briefly suffer redness or peeling.

6.4 Gastrointestinal Issues: Ingesting bakuchiol may result in nausea, vomiting, and gastritis. [103]

When using large dosages or continuous use, especially when sourced from the Psoraleae Fructus source, there are worries about liver damage.
For women who are expecting or nursing, caution is suggested because safety during these times is not well established. [104,105]

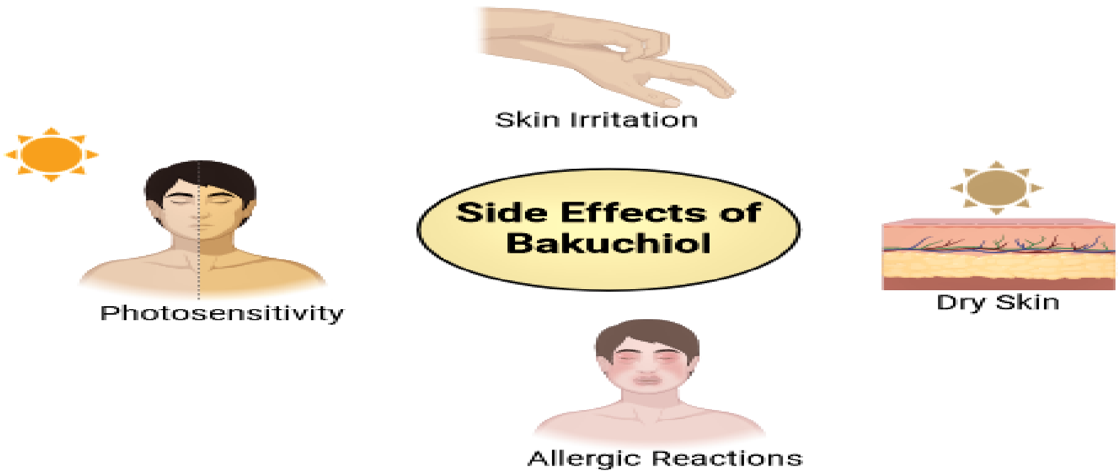


Fig.6.1 Side Effects of Bakuchiol

7. CONCLUSION:

Bakuchiol is a potentially useful component for skincare products that is extracted from Psoralea corylifolia seeds. It provides a strong substitute for conventional anti-aging ingredients because of its capacity to lessen fine wrinkles, enhance skin texture, and lessen hyperpigmentation. Bakuchiol is soft on the skin, making it appropriate for sensitive people, in contrast to certain strong treatments. In addition to promoting general skin health, its anti-inflammatory qualities shield the skin from environmental harm. Even though study backs up the advantages of bakuchiol, more research is required to maximize its application in cosmetics. Bakuchiol's gentle nature and established effectiveness position it as a major participant in the beauty market as consumer interest in natural and effective skincare rises. This plant-based substance has the potential to transform skincare regimens and produce healthier, more youthful-looking skin with more research.
In conclusion, Bakuchiol stands out among ingredients in the pursuit of healthier, more youthful skin due to its shown cosmetic advantages and mild profile, which promises to satisfy the changing needs of contemporary skincare customers.

6. REFERENCES:

[1]. Mascarenhas-Melo F, Ribeiro MM, Kahkesh KH, Parida S, Pawar KD, Velsankar K, Jha NK, Damiri F, Costa G, Veiga F, Paiva-Santos AC. Comprehensive review of the skin use of bakuchiol: physicochemical properties, sources, bioactivities, nanotechnology delivery systems, regulatory and toxicological concerns. Phytochemistry Reviews. 2024 Mar 1:1-37.

[2]. Alam F, Khan GN, Asad M (2018) Psoralea corylifolia L: ethnobotanical, biological, and chemical aspects: a review. Phytother Res PTR 32(4):597–615.

[3]. Van Wyk AS, Prinsloo G. Medicinal plant harvesting, sustainability and cultivation in South Africa. Biological Conservation. 2018 Nov 1; 227:335-42.

[4]. Choi SY, Lee S, Choi WH, Lee Y, Jo YO, Ha TY. Isolation and anti-inflammatory activity of Bakuchiol from Ulmus avidiana var. japonica. Journal of medicinal food. 2010 Aug 1;13(4):1019-23.

[5]. Haraguchi H, Inoue J, Tamura Y, Mizutani K. Inhibition of mitochondrial lipid peroxidation by bakuchiol, a meroterpene from Psoralea corylifolia. Planta medica. 2000 Aug;66(06):569-71.

[6]. Puyana C, Chandan N, Tsoukas M. Applications of bakuchiol in dermatology: Systematic review of the literature. Journal of cosmetic dermatology. 2022 Dec;21(12):6636-43.

[7]. Agarwal, M., Singh, A., Mathur, N., Sharma, S.J.I.J.o.S., Research, T. Comparative Study Of Synthetic And Herbal Cosmetic Products For Their Toxicity Assessment By Microbial Bioassays. 2019, 8, 1128-1133.

[8].Goyal, A., Sharma, A., Kaur, J., Kumari, S., Garg, M., Sindhu, R.K., Rahman, M.H., Akhtar, M.F., Tagde, P., Najda, A., Banach-Albinska, B., Masternak, K., Alanazi, I.S., Mohamed, H.R.H., El-Kott, A.F., Shah, M., Germoush, M.O., Al-Malky, H.S., Abukhuwayjah, S.H., Altyar, A.E., Bungau, S.G., Abdel-Daim, M.M. Bioactive-Based Cosmeceuticals: An Update on Emerging Trends. Molecules 2022, 27

[9]. Mahajan N, Koul B, Gupta P, Shah BA, Singh J. Psoralea corylifolia L.: Panacea to several maladies. South African Journal of Botany. 2022 Sep 1;149:963-93.

[10]. Adarsh Krishna TP, Edachery B, Athalathil S, et al.: Bakuchiol - a natural meroterpenoid: structure, isolation, synthesis and functionalization approaches. 2022 Mar;12(14):8815–8832.

[11]. Husain FM, Ahmad I, Khan MS, Al-Shabib NA. Trigonella foenum-graceum (Seed) extract interferes with quorum sensing regulated traits and biofilm formation in the strains of Pseudomonas aeruginosa and Aeromonas hydrophila. Evidence-Based Complementary and Alternative Medicine. 2015;2015(1):879540.

[12]. McLean RJ, Pierson III LS, Fuqua C. A simple screening protocol for the identification of quorum signal antagonists. Journal of microbiological methods. 2004 Sep 1;58(3):351-60.

[13]. Chopra RN, Chopra IC. Chopra's indigenous drugs of India. Academic publishers; 2006.

[14]. Panda H. Herbs cultivation and medicinal uses. National Institute of Industrial Research; 1999.

[15]. Limper C, Wang Y, Ruhl S, Wang Z, Lou Y, Totzke F, Kubbutat MH, Chovolou Y, Proksch P, Wätjen W. Compounds isolated from Psoralea corylifolia seeds inhibit protein kinase activity and induce apoptotic cell death in mammalian cells. Journal of Pharmacy and Pharmacology. 2013 Sep;65(9):1393-408.

[16]. Banerji A, Chintalwar GJ. Biosynthesis of bakuchiol, a meroterpene from Psoralea corylifolia. Phytochemistry. 1983 Jan 1;22(9):1945-7.

[17]. Murray RD, Jorge ZD, Lawrie KW. Claisen rearrangements—X: Synthesis of the coumarins, hortiolone and hortinone. Tetrahedron. 1983 Jan 1;39(19):3159-62.

[18]. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. International journal of molecular sciences. 2019 Nov 28;20(23):6008.

[19]. Ferrándiz ML, Gil B, Sanz MJ, Ubeda A, Erazo S, González E, Negrete R, Pacheco S, Payáa M, Alcaraz MJ. Effect of bakuchiol on leukocyte functions and some inflammatory responses in mice. Journal of pharmacy and pharmacology. 1996 Sep;48(9):975-80.

[20]. Lim HS, Kim YJ, Kim BY, Jeong SJ. Bakuchiol suppresses inflammatory responses via the downregulation of the p38 MAPK/ERK signaling pathway. International journal of molecular sciences. 2019 Jul 22;20(14):3574.

[21]. Lee SW, Yun BR, Kim MH, Park CS, Lee WS, Oh HM, Rho MC. Phenolic compounds isolated from Psoralea corylifolia inhibit IL-6-induced STAT3 activation. Planta Medica. 2012 Jun;78(09):903-6.

[22]. Zafar SK, Iqbal S, Mumtaz M, Ali SK, Ali ST. Inhibitory mechanism exhibited by phenol-based natural products against DNA polymerase [alpha] from Psoralea corylifolia by molecular docking. J Chem Soc Pak. 2018 Jan;40(6):1089-92.

[23]. Chen Z, Jin K, Gao L, Lou G, Jin Y, Yu Y, Lou Y. Anti-tumor effects of bakuchiol, an analogue of resveratrol, on human lung adenocarcinoma A549 cell line. European journal of pharmacology. 2010 Sep 25;643(2-3):170-9.

[24]. Zouhiri F, Danet M, Bénard C, Normand-Bayle M, Mouscadet JF, Leh H, Thomas CM, Mbemba G, d'Angelo J, Desmaële D. HIV-1 replication inhibitors of the styrylquinoline class: Introduction of an additional carboxyl group at the C-5 position of the quinoline. Tetrahedron Letters. 2005 Mar 28;46(13):2201-5.

[25]. Rocha-Pereira J, Cunha R, Pinto DC, Silva AM, Nascimento MS. (E)-2-Styrylchromones as potential anti-norovirus agents. Bioorganic & medicinal chemistry. 2010 Jun 15;18(12):4195-201.

[26]. Lee IK, Han MS, Lee MS, Kim YS, Yun BS. Styrylpyrones from the medicinal fungus Phellinus baumii and their antioxidant properties. Bioorganic & Medicinal Chemistry Letters. 2010 Sep 15;20(18):5459-61.

[27]. Xu K, Sha Y, Wang S, Chi Q, Liu Y, Wang C, Yang L. Effects of Bakuchiol on chondrocyte proliferation via the PI3K-Akt and ERK1/2 pathways mediated by the estrogen receptor for promotion of the regeneration of knee articular cartilage defects. Cell proliferation. 2019 Sep;52(5):e12666.

[28]. Majeed R, Reddy MV, Chinthakindi PK, Sangwan PL, Hamid A, Chashoo G, Saxena AK, Koul S. Bakuchiol derivatives as novel and potent cytotoxic agents: A report. European journal of medicinal chemistry. 2012 Mar 1;49:55-67.

[29]. Pop C, Salvesen GS. Human caspases: activation, specificity, and regulation. Journal of biological Chemistry. 2009 Aug 14;284(33):21777-81.

[30]. Berthelet J, Dubrez L. Regulation of apoptosis by inhibitors of apoptosis (IAPs). Cells. 2013 Mar 14;2(1):163-87.

[31]. Mace PD, Shirley S, Day CL. Assembling the building blocks: structure and function of inhibitor of apoptosis proteins. Cell Death & Differentiation. 2010 Jan;17(1):46-53.

[32]. Müschen M, Beckmann MW. CD95 ligand expression as a criterion of malignant transformation in breast cancer. The Journal of Pathology. 2000 Aug 1;191(4):468-70.

[33]. Tourneur L, Buzyn A, Chiocchia G. FADD adaptor in cancer. Medical Immunology. 2005 Dec;4:1-9.

[34].Müschen M, Rajewsky K, Krönke M, Küppers R. The origin of CD95-gene mutations in B-cell lymphoma. Trends in immunology. 2002 Feb 1;23(2):75-80.

[35]. Tourneur L, Delluc S, Lévy V, Valensi F, Radford-Weiss I, Legrand O, Vargaftig J, Boix C, Macintyre EA, Varet B, Chiocchia G. Absence or low expression of fas-associated protein with death domain in acute myeloid leukemia cells predicts resistance to chemotherapy and poor outcome**.** Cancer research. 2004 Nov 1;64(21):8101-8.

[36]. Teitz T, Wei T, Valentine MB, Vanin EF, Grenet J, Valentine VA, Behm FG, Look AT, Lahti JM, Kidd VJ. Caspase 8 is deleted or silenced preferentially in childhood neuroblastomas with amplification of MYCN. Nature medicine. 2000 May;6(5):529-35.

[37]. Gandour-Edwards R, Mack PC, Devere-White RW, Gumerlock PH. Abnormalities of apoptotic and cell cycle regulatory proteins in distinct histopathologic components of benign prostatic hyperplasia. Prostate Cancer and Prostatic Diseases. 2004 Dec;7(4):321-6.

[38]. Watanabe A, Yasuhira S, Inoue T, Kasai S, Shibazaki M, Takahashi K, Akasaka T, Masuda T, Maesawa C. BCL 2 and BCL xL are key determinants of resistance to antitubulin chemotherapeutics in melanoma cells. Experimental Dermatology. 2013 Aug;22(8):518-23.

[39]. Raffo AJ, Perlman H, Chen MW, Day ML, Streitman JS, Buttyan R. Overexpression of bcl-2 protects prostate cancer cells from apoptosis in vitro and confers resistance to androgen depletion in vivo**.** Cancer research. 1995 Oct 1;55(19):4438-45.

[40]. Fulda S, Meyer E, Debatin KM. Inhibition of TRAIL-induced apoptosis by Bcl-2 overexpression. Oncogene. 2002 Apr;21(15):2283-94.

[41]. Foreman KE, Wrone-Smith T, Boise LH, Thompson CB, Polverini PJ, Simonian PL, Nunez G, Nickoloff BJ. Kaposi's sarcoma tumor cells preferentially express Bcl-xL. The American journal of pathology. 1996 Sep;149(3):795.

[42]. Krajewska M, Moss SF, Krajewski S, Song KI, Holt PR, Reed JC. Elevated expression of Bcl-X and reduced Bak in primary colorectal adenocarcinomas**.** Cancer Research**.** 1996 May 15;56(10):2422-7.

[43]. Minn AJ, Rudin CM, Boise LH, Thompson CB. Expression of bcl-xL can confer a multidrug resistance phenotype. Blood. 1995 Sep 1;86(5):1903-10.

[44]. Han JY, Hong EK, Choi BG, Park JN, Kim KW, Kang JH, Jin JY, Park SY, Hong YS, Lee KS. Death receptor 5 and Bcl-2 protein expression as predictors of tumor response to gemcitabine and cisplatin in patients with advanced non-small-cell lung cancer. Medical oncology. 2003 Dec;20:355-62.

[45]. Soengas MS, Capodieci P, Polsky D, Mora J, Esteller M, Opitz-Araya X, McCombie R, Herman JG, Gerald WL, Lazebnik YA, Cordón-Cardó C. Inactivation of the apoptosis effector Apaf-1 in malignant melanoma. Nature. 2001 Jan 11;409(6817):207-11.

[46]. Baldi A, Santini D, Russo P, Catricalà C, Amantea A, Picardo M, Tatangelo F, Botti G, Dragonetti E, Murace R, Tonini G. Analysis of APAF-1 expression in human cutaneous melanoma progression. Experimental dermatology. 2004 Feb;13(2):93-7.

[47]. Pepper C, Hoy T, Bentley DP. Bcl-2/Bax ratios in chronic lymphocytic leukaemia and their correlation with in vitro apoptosis and clinical resistance. British Journal of Cancer. 1997 Oct;76(7):935-8.

[48]. Miquel C, Borrini F, Grandjouan S, Aupérin A, Viguier J, Velasco V, Duvillard P, Praz F, Sabourin JC. Role of bax mutations in apoptosis in colorectal cancers with microsatellite instability. American journal of clinical pathology. 2005 Apr 1;123(4):562-70.

[49]. Schimmer AD. Inhibitor of apoptosis proteins: translating basic knowledge into clinical practice. Cancer research. 2004 Oct 15;64(20):7183-90.

[50]. Fulda S. Inhibitor of apoptosis proteins in hematological malignancies. Leukemia. 2009 Mar;23(3):467-76.

[51]. Soengas MS, Capodieci P, Polsky D, Mora J, Esteller M, Opitz-Araya X, McCombie R, Herman JG, Gerald WL, Lazebnik YA, Cordón-Cardó C. Inactivation of the apoptosis effector Apaf-1 in malignant melanoma. Nature. 2001 Jan 11;409(6817):207-11.

[52]. Fulda S, Debatin KM. IFNγ sensitizes for apoptosis by upregulating caspase-8 expression through the Stat1 pathway. Oncogene. 2002 Apr;21(15):2295-308.

[53]. Almasan A, Ashkenazi A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy. Cytokine & growth factor reviews. 2003 Jun 1;14(3-4):337-48.

[54]. Amarante-Mendes GP, Griffith TS. Therapeutic applications of TRAIL receptor agonists in cancer and beyond. Pharmacology & therapeutics. 2015 Nov 1;155:117-31.

[55]. Pae HO, Cho H, Oh GS, Kim NY, Song EK, Kim YC, Yun YG, Kang CL, Kim JD, Kim JM, Chung HT. Bakuchiol from Psoralea corylifolia inhibits the expression of inducible nitric oxide synthase gene via the inactivation of nuclear transcription factor-κB in RAW 264.7 macrophages. International immunopharmacology. 2001 Sep 1;1(9-10):1849-55.

[56]. Choi SY, Lee S, Choi WH, Lee Y, Jo YO, Ha TY. Isolation and anti-inflammatory activity of Bakuchiol from Ulmus davidiana var. japonica. Journal of medicinal food. 2010 Aug 1;13(4):1019-23.

[57]. Ferrándiz ML, Gil B, Sanz MJ, Ubeda A, Erazo S, González E, Negrete R, Pacheco S, Payáa M, Alcaraz MJ. Effect of bakuchiol on leukocyte functions and some inflammatory responses in mice. Journal of pharmacy and pharmacology. 1996 Sep;48(9):975-80.

[58]. Zhou B, Yang Z, Feng Q, Liang X, Li J, Zanin M, Jiang Z, Zhong N. Aurantiamide acetate from baphicacanthus cusia root exhibits anti-inflammatory and anti-viral effects via inhibition of the NF-κB signaling pathway in Influenza A virus-infected cells. Journal of ethnopharmacology. 2017 Mar 6;199:60-7.

[59]. Lim HS, Kim YJ, Kim BY, Jeong SJ. Bakuchiol suppresses inflammatory responses via the downregulation of the p38 MAPK/ERK signaling pathway. International journal of molecular sciences. 2019 Jul 22;20(14):3574.

[60]. Xu Q, Lv Q, Liu L, Zhang Y, Yang X. New bakuchiol dimers from Psoraleae Fructus and their inhibitory activities on nitric oxide production. Chinese Medicine. 2021 Dec;16:1-5.

[61]. Brandt SL, Serezani CH. Too much of a good thing: How modulating LTB4 actions restore host defense in homeostasis or disease. InSeminars in immunology 2017 Oct 1 (Vol. 33, pp. 37-43). Academic Press.

[62]. Woo CH, You HJ, Cho SH, Eom YW, Chun JS, Yoo YJ, Kim JH. Leukotriene B4 stimulates Rac-ERK cascade to generate reactive oxygen species that mediates chemotaxis. Journal of Biological Chemistry. 2002 Mar 8;277(10):8572-8.

[63]. Truong CS, Seo E, Jun HS. Psoralea corylifolia L. Seed Extract Attenuates Methylglyoxal-Induced Insulin Resistance by Inhibition of Advanced Glycation End Product Formation. Oxidative Medicine and Cellular Longevity. 2019;2019(1):4310319.

[64].Stéphane FF, Jules BK, Batiha GE, Ali I, Bruno LN. Extraction of bioactive compounds from medicinal plants and herbs. Natural medicinal plants. 2021 Aug 27:1-39.

[65]. Nam SW, Baek JT, Lee DS, Kang SB, Ahn BM, Chung KW. A case of acute cholestatic hepatitis associated with the seeds of Psoralea corylifolia (Boh-Gol-Zhee). Clinical Toxicology. 2005 Jan 1;43(6):589-91.

[66]. Li YJ, Huang YY. Drug-induced liver injury caused by Psoralea corylifolia: a case report. Shanghai Med. Pharm. 2016;37(24):41-2.

[67]. Zhang QW, Lin LG, Ye WC. Techniques for extraction and isolation of natural products: A comprehensive review. Chinese medicine. 2018 Dec;13:1-26.

[68]. Li P, Xu G, Li SP, Wang YT, Fan TP, Zhao QS, Zhang QW. Optimizing ultraperformance liquid chromatographic analysis of 10 diterpenoid compounds in Salvia miltiorrhiza using central composite design. Journal of agricultural and food chemistry. 2008 Feb 27;56(4):1164-71.

[69].Krishna TA, Edachery B, Athalathil S. Bakuchiol–a natural meroterpenoid: structure, isolation, synthesis and functionalization approaches. RSC advances. 2022;12(14):8815-32.

[70]. Chi M, Peng Y, Zheng J. Characterization of glutathione conjugates derived from reactive metabolites of bakuchiol. Chemico-Biological Interactions. 2016 Jan 25;244:178-86.

[71]. Gao F, McGrath KP, Lee Y, Hoveyda AH. Synthesis of quaternary carbon stereogenic centers through enantioselective Cu-catalyzed allylic substitutions with vinylaluminum reagents. Journal of the American Chemical Society. 2010 Oct 13;132(40):14315-20.

[72]. Takao KI, Sakamoto S, Touati MA, Kusakawa Y, Tadano KI. Asymmetric construction of all-carbon quaternary stereocenters by chiral-auxiliary-mediated Claisen rearrangement and total synthesis of (+)-bakuchiol. Molecules. 2012 Nov 8;17(11):13330-44.

[73].Dang TT, Van Vuong Q, Schreider MJ, Bowyer MC, Van Altena IA, Scarlett CJ. Optimisation of ultrasound-assisted extraction conditions for phenolic content and antioxidant activities of the alga Hormosira banksii using response surface methodology. Journal of Applied Phycology. 2017 Dec;29:3161-73.

[74]. Rahimi F, Tabarsa M, Rezaei M. Ulvan from green algae Ulva intestinalis: Optimization of ultrasound-assisted extraction and antioxidant activity. Journal of Applied Phycology. 2016 Oct;28:2979-90.

[75]. Vázquez-Rodríguez B, Gutiérrez-Uribe JA, Antunes-Ricardo M, Santos-Zea L, Cruz-Suárez LE. Ultrasound-assisted extraction of phlorotannins and polysaccharides from Silvetia compressa (Phaeophyceae). Journal of applied phycology. 2020 Apr;32:1441-53.

[76]. Tiwari BK. Ultrasound: A clean, green extraction technology. TrAC Trends in Analytical Chemistry. 2015 Sep 1;71:100-9.

[77]. Saien J, Daneshamoz S. Experimental studies on the effect of ultrasonic waves on single drop liquid–liquid extraction. Ultrasonics sonochemistry. 2018 Jan 1;40:11-6.

[78]. Kentish S, Ashokkumar M. The Physical and Chemical Effects of Ultrasound. In (Eds): Feng H., Barbosa-Canovas GV, Weiss J. Ultrasound Technologies for Food and Bioprocessing.

[79]. Cavalieri F, Chemat F, Okitsu K, Sambandam A, Yasui K, Zisu B. Handbook of ultrasonics and sonochemistry. Springer; 2018 Feb 11.

[80]. Chemat F, Rombaut N, Sicaire AG, Meullemiestre A, Fabiano-Tixier AS, Abert-Vian M. Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review. Ultrasonics sonochemistry. 2017 Jan 1;34:540-60.

[81]. Cravotto G, Boffa L, Mantegna S, Perego P, Avogadro M, Cintas P. Improved extraction of vegetable oils under high-intensity ultrasound and/or microwaves. Ultrasonics sonochemistry. 2008 Jul 1;15(5):898-902.

[82]. Esclapez MD, Sáez V, Milán-Yáñez D, Tudela I, Louisnard O, González-García J. Sonoelectrochemical treatment of water polluted with trichloroacetic acid: from sonovoltammetry to pre-pilot plant scale. Ultrasonics sonochemistry. 2010 Aug 1;17(6):1010-20.

[83]. Huang G, Chen F, Yang W, Huang H. Preparation, deproteinization and comparison of bioactive polysaccharides. Trends in Food Science & Technology. 2021 Mar 1;109:564-8.

[84]. Li R, Xia Z, Li B, Tian Y, Zhang G, Li M, Dong J. Advances in supercritical carbon dioxide extraction of bioactive substances from different parts of Ginkgo biloba L. Molecules. 2021 Jun 30;26(13):4011.

[85]. Jiang S, Liu S, Qin M. Effects of extraction conditions on crude polysaccharides and antioxidant activities of the lion's mane medicinal mushroom, Hericium erinaceus (Agaricomycetes). International Journal of Medicinal Mushrooms. 2019;21(10).

[86]. You Q, Yin X, Zhao Y. Enzyme assisted extraction of polysaccharides from the fruit of Cornus officinalis. Carbohydrate polymers. 2013 Oct 15;98(1):607-10.

[87]. Ahmad MM, Chatha SA, Iqbal Y, Hussain AI, Khan I, Xie F. Recent trends in extraction, purification, and antioxidant activity evaluation of plant leaf-extract polysaccharides. Biofuels, Bioproducts and Biorefining. 2022 Nov;16(6):1820-48.

[88]. Chen R, Li Y, Dong H, Liu Z, Li S, Yang S, Li X. Optimization of ultrasonic extraction process of polysaccharides from Ornithogalum Caudatum Ait and evaluation of its biological activities. Ultrasonics Sonochemistry. 2012 Nov 1;19(6):1160-8.

[89]. Huang H, Huang G. Extraction, separation, modification, structural characterization, and antioxidant activity of plant polysaccharides. Chemical biology & drug design. 2020 Nov;96(5):1209-22.

[90]. Xie JH, Shen MY, Nie SP, Zhao Q, Li C, Xie MY. Separation of water-soluble polysaccharides from Cyclocarya paliurus by ultrafiltration process. Carbohydrate polymers. 2014 Jan 30;101:479-83.

[91]. Tang HL, Chen C, Wang SK, Sun GJ. Biochemical analysis and hypoglycemic activity of a polysaccharide isolated from the fruit of Lycium barbarum L. International Journal of Biological Macromolecules. 2015 Jun 1;77:235-42.

[92]. Dias AL, de Aguiar AC, Rostagno MA. Extraction of natural products using supercritical fluids and pressurized liquids assisted by ultrasound: Current status and trends. Ultrasonics Sonochemistry. 2021 Jun 1;74:105584.

[93].Priyanto, Olivia Jovina; Sugiyanto, Yosef Ferdinand Rahmat; and Salim, Darryl Samuel (2023) "The effect of bakuchiol in the skin aging process: A systematic review," Journal of General - Procedural Dermatology & Venereology Indonesia: Vol. 7: Iss. 2, Article 9.

[94].Edgar S, Hopley B, Genovese L, Sibilla S, Laight D, Shute J. Effects of collagen-derived bioactive peptides and natural antioxidant compounds on proliferation and matrix protein synthesis by cultured normal human dermal fibroblasts. Scientific Reports. 2018 Jul 11;8(1):10474.

[95]. Zouboulis CC, Makrantonaki E, Nikolakis G. When the skin is in the center of interest: An aging issue. Clinics in dermatology. 2019 Jul 1;37(4):296-305.

[96]. RK Chaudhuri, R Sharma, KR Ranganathan,G Gutierrez and M Serrar, Is plant-derived meroterpene an effective replacement of retin-oid for the treatment of acne-affected skin?proceedings of 25th IFSCC, Barcelona, Spain 3 65–70 (2008)

[97]. Anwar, A.I.; Wahab, S.; Widita, W.; Nurdin, A.R.; Budhiani, S.; Seweng, A. Randomized control trial outcomes of tranexamic acid combination serum as a depigmenting agent for the use in healthy individuals. Dermatol. Ther. 2019.

[98]. Draelos ZD, Gunt H, Zeichner J, et al.: Clinical Evaluation of a Nature-Based Bakuchiol Anti-Aging Moisturizer for Sensitive Skin. J Drugs Dermatol. 2020 Dec;19(12):1181–1183.

[99]. Bacqueville D, Maret A, Noizet M, et al.: Efficacy of a Dermocosmetic Serum Combining Bakuchiol and Vanilla Tahitensis Extract to Prevent Skin Photoaging in vitro and to Improve Clinical Outcomes for Naturally Aged Skin. Clin. Cosmet. Investig. Dermatol. 2020;13:359–370.

[100]. Li CC, Wang TL, Zhang ZQ, Yang WQ, Wang YF, Chai X, Wang CH, Li Z. Phytochemical and pharmacological studies on the genus psoralea: a mini review. Evidence-Based Complementary and Alternative Medicine. 2016;2016(1):8108643.

[101]. Kibe MN, Konyole S, Nguka G, Oloo MO, Kathure D, Wangari PM. The role of phytochemicals in prevention and control of chronic diseases. International Journal of Current Research. 2017;9(12):62540-3.

[102]. Adhikari S, Joshi R, Patro BS, et al. Antioxidant activity of bakuchiol: experimental evidences and theoretical treatments on the possible involvement of the terpenoid chain. Chem Res Toxicol. 2003;16(9):1062-1069.

[103]. Chaudhuri RK, Bojanowski K. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. Int J Cosmet Sci. 2014;36(3):221-230. doi:10.1111/ics.12117

[104]. Nam SW, Baek JT, Lee DS, et al.: A case of acute cholestatic hepatitis associated with the seeds of Psoralea corylifolia (Boh-Gol-Zhee). Clin. Toxicol. (Phila.). 2005;43(6):589–591.

[105]. Zouboulis, C.C., Eady, A., Philpott, M., Goldsmith, L.A., Orfanos, C., Cunliffe, W.C., Rosenfield, R. What is the pathogenesis of acne? Exp Dermatol 2005, 14, 143-152.