



REVIEW

Bakuchiol and its pharmacological benefits [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background and aims: Natural compounds extracted from medicinal plants have recently gained attention in therapeutics as they are considered to have lower toxicity and higher tolerability relative to chemically synthesized compounds. Bakuchiol is one such compound; it is a type of meroterpene derived from the leaves and seeds of *Psoralea corylifolia* plants. Natural sources of bakuchiol have been used in traditional Chinese and Indian medicine for centuries due to its preventive benefits against tumors and inflammation. It plays a strong potential role as an antioxidant with impressive abilities to remove Reactive Oxygen Species (ROS). This review has focused on bakuchiol's extraction, therapeutic applications, and pharmacological benefits.

Methods: A search strategy has been followed to retrieve the relevant newly published literature on the pharmacological benefits of bakuchiol. After an extensive study of the retrieved articles and maintaining the inclusion and exclusion criteria, 106 articles were finally selected for this review.

Results: Strong support of primary research on the protective effects via antitumorigenic, anti-inflammatory, antioxidative, antimicrobial, and antiviral activities are delineated.

Conclusions: From ancient to modern life, medicinal plants have always been drawing the attention of human beings to alleviate ailments for a healthy and balanced lifestyle. This review is a comprehensive approach to highlighting bona fide essential pharmacological benefits and mechanism of action of therapeutic implications.

Keywords

Bakuchiol, *Psoralea corylifolia*, medicinal plants, health benefits

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List of abbreviations

3-NT: 3 Nitrotyrosine
 4HNE: 4-Hydroxynonenal
 AKT: Protein kinase B
 AMPK: AMP-activated protein kinase
 AR: Androgen receptor
 ATM: Ataxia-Telangiectasia Mutated Kinase
 ATM: ATM serine/threonine kinase
 BAK: Bakuchiol
 Bax: Bcl-2-associated X protein
 Bcl2: B-cell lymphoma 2
 Cdc2: Cell division control 2
 Col I: Collagen type I
 Col III: Collagen type III
 COX2: Cyclooxygenase2
 ER-alpha: Estrogen Receptor alpha
 ER-beta: Estrogen Receptor beta
 GSH-Pxi: Inducible Glutathione peroxidase
 GSTA3: Glutathione S-Transferase Alpha 3
 HIF-1: Hypoxia-inducible factor 1
 H1N1: Hemagglutinin 1 neuraminidase 1
 HNO₃: Nitric acid
 IL6: Interleukin 6
 iNOS: Inducible Nitric Oxide Synthase
 LTB4: Leukotriene B4
 LPS: Lipopolysaccharide
 MDA: Malondialdehyde
 MAPK: Mitogen-activated protein kinases
 MMP-1: Matrix metalloproteinase-1
 Myt1: Myelin Transcription Factor 1
 NFkB: Nuclear Factor kappa-light-chain-enhancer of activated B cells
 NQ01: NAD(P)H Quinone Dehydrogenase 1
 NSCLC: Non-small cell lung cancer
 Nrf1: Nuclear Respiratory Factor 1
 p38: Tumor protein p53
 PGC-1 α : Proliferator-activated receptor gamma coactivator 1-alpha
 PGE2: Prostaglandin E2
 P-Cdc2: Phosphorylated cell division cycle protein 2
 Rac: Ras-related C3 botulinum toxin
 ROS: Reactive Oxygen Species
 SARS-CoV-2: Severe Acute Respiratory Syndrome-CoronaVirus-2
 Sirt1: NAD-dependent deacetylase sirtuin-1
 STAT3: Signal transducer and activator of transcription 3
 SOD: Superoxide Dismutase
 TIMP-1: Tissue inhibitors of metalloproteinases-1
 TIMP-2: Tissue inhibitors of metalloproteinases-2
 TNF α : Tumour Necrosis Factor alpha
 Trx1: Thioredoxin 1
 TXNIP: Thioredoxin-interacting protein

Introduction

Plants have been used in traditional Indian and Oriental medicine for centuries. Despite improved access to essential medicines as supported by World Health Organization (WHO),¹ a large population, especially in less developed countries, still relies on plant-based medications for primary health care needs due to ease of availability and high benefit to cost ratio.² There is an increase in global demand for medicinal plants due to improved quality of life. Some compounds have been extracted from these beneficial plants to study their mechanisms of action that facilitate their beneficial effects.

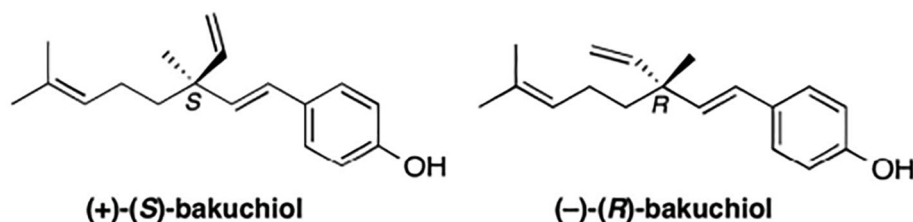


Figure 1. Chemical Structures of naturally occurring (+)-(S)-Bakuchiol and its enantiomer (R)-(-)-Bakuchiol. This figure has been adapted from Khuranna *et al.*¹⁴ under CC BY 4.0.

Bakuchiol, extracted predominantly and traditionally from the *Psoralea corylifolia* L. plant, is one such compound. It is a meroterpene that has shown potent antimicrobial, anti-inflammatory, anti-osteoporotic, and antitumorigenic activities and exhibited other beneficial uses.³ It has also gained huge popularity in the beauty industry as a tolerable analogue of retinol in skin therapeutics.⁴ Studies have also shown bakuchiol's protective effect on the liver, heart, bones, and other organs.⁵ Recent studies have focused on bakuchiol and its therapeutic effects, showing promise as a multi-targeting therapeutic agent.^{6–13}

Bakuchiol is a naturally occurring prenylated phenolic isoprenoid (Figure 1). It is a type of meroterpene with a chiral tetra-alkylated (all-carbon) quaternary center.¹⁵ It was first extracted from the seeds of *Psoralea corylifolia* in 1966 when its plane structure was also determined, while its configuration of the quaternary center was determined in 1973.¹⁶ The formal chemical name of bakuchiol is 4-[(1E,3S)-3-ethenyl-3,7-dimethyl-1,6-octadien-1-yl]-phenol. Its naturally occurring form (S)-(+)-Bakuchiol has an enantiomer (R)-(-)-Bakuchiol, and its chirality influences their actions and effectiveness.

The source of bakuchiol varies between regions; it is commonly extracted from the seeds and leaves of *Psoralea corylifolia* (Babchi plant) in India, which belongs to the Leguminosae plant family, and is a major phytochemical present in the root and stem of *Ulmus davidiana* var.¹⁷ *Japonica* (Japanese Elm) is widely distributed in China, Japan, and Korea.⁶ These plants have been used in their regions of wide distribution in traditional medicine to treat inflammatory disorders and cancer. *Piper longum* (Long pepper), *Psoralea glandulosa* L., *Otholobium pubescens*, *Prosopis glandulosa*, *Aerva sanguinolenta*, *Psoralidium tenuiflorum*, *Pimelea drupacea*, *Bridelia retusa*, *Spiraea formosana*, *Elaeagnus bockii* and other sources of bakuchiol have been discovered in recent times.^{18–20}

Medicinal plants e.g.: *Psoralea corylifolia* where bakuchiol is derived have been used directly as traditional medication or via pharmaceutical preparations in modern medicine. Recent times have shown collective evidence highlighting the immense potential of traditionally used medicinal plants and their derived compounds.²¹ An increase in international demand and trade has also been observed, appreciating its low costs and tolerability. In addition, an increasing trend of antimicrobial resistance has been observed due to inappropriate dosage and lack of regulation of prescriptions. It is thus imperative to find new sources of antiviral and antimicrobial therapy to account for the increased resistance observed. Plants and phytochemicals are generally considered sources of tolerable, less toxic treatments.²¹ Bakuchiol has recently been studied in detail in research settings while being used in traditional medicine for centuries.²²

This review article focuses on the potential pharmacological benefits of bakuchiol, focusing on its promising protective effects in controlling activities that lead to the amelioration of non-communicable diseases, as well as verifying its function as an antimicrobial and antiviral agent. The workflow of this review is illustrated in Figure 2. The knowledge gained from this review will shed light on the published research to pave the path for future research perspectives and considerations.

Methods

Retrieval of the published articles

This review evaluates the pharmacological uses of bakuchiol, focusing on its promising protective effects on controlling both communicable and non-communicable diseases. Data for this study have been amalgamated from both primary and secondary data resources, including clinical trials (both randomized and non-randomized), as well as *in vitro* and *in vivo* studies, which have evaluated the use of bakuchiol as a potential pharmacological agent in controlling multiple disease conditions.

Several inclusion and exclusion criteria were fixed while selecting articles for this review. The works done from 1990 to 2022 have been studied rigorously. Literature searches were done using the keywords such as “*Psoralea corylifolia*

Psoralea corylifolia



Data Mining: Browse existing literature to learn its diverse implications

Data Sorting: Classify the gathered information into different pharmacological application

Data Analyzing: Correlated various experiments with their relevant pharmacological implication to support a claim with scientific validation

Data Interpretation and Reproduction: Based on the gathered evidences, projected possible future use and scope of further experimental validation

Figure 2. Workflow of the study. This figure is an original figure produced by the author(s) for this review article. The image of *Psoralea corylifolia* has been reproduced from Niu *et al.*²³ under CC BY-NC 3.0.

AND/OR Babchi AND/OR Bakuchiol” in various available online scientific databases. Articles that represent phytochemistry AND/OR pharmacological activity AND/OR health benefits of Bakuchiol published in PubMed, Web of Science, PMC, Google Scholar, ScienceDirect, and ResearchGate were incorporated in this review. From the evaluation of 106 articles, the effect of bakuchiol as a potential antitumorigenic, anti-inflammatory, antioxidative, antimicrobial, and antiviral agents, as characterized in several studies, was finally assessed for this review. In addition, clinical trial databases were also searched to find current registered clinical trials of the use of bakuchiol in multiple disorders, including diabetes, inflammatory disorders of the skin and other organs, oral disorders, cancer, and coronavirus disease 2019 (COVID-19). Only articles published in English were considered for this review. The databases were searched in a timeline from 2010 to date, except for articles related to its initial discovery and extraction, and only approved and published data were considered for this review unless otherwise mentioned. In most studies, the outcomes measured and considered for this review include the severity and comparative assessment of disease progression in bakuchiol-treated and untreated groups.

Results

Extraction and solubility of Bakuchiol

Traditional plant-based medications work by grinding the interest portion and then extracting it into carrier oils or spirits.²⁴ However, specific compounds cannot be distilled this way and there may also be the presence of potentially cytotoxic compounds in an extract made in traditional methods.^{25,26} While beneficial, the number of bioactive ingredients present in natural sources is generally meager, and extraction processes are time-consuming and lab-intensive, hindering the mass-scale use of natural products in drug selection and development. Current extraction methods include distillation, cold pressing for oils, and solvent extraction, the most commonly used method.²⁷

Factors that affect the ease of solubility and diffusivity are considered during extraction processes, including consideration of the properties of the solvent being used, such as the laws of inter miscibility as well as cost and safety, the size of the raw materials material being used, temperature and time duration.²⁷ Generally, methanol and ethanol are used in solvent extraction for phytochemicals. Smaller particle sizes of raw materials are preferred for better extraction efficiency.²⁸ Temperature is also an essential factor in controlling the extraction rate, as higher temperatures increase solubility and diffusion, but this is not ideal for highly volatile compounds as higher temperatures can cause the decomposition of thermolabile compounds.²⁹

Bakuchiol is soluble in organic solvents such as ethanol and dimethyl sulfoxide (DMSO) and sparingly soluble in aqueous solutions.⁶ Its solubility can be increased by first making a stock solution with ethanol and then diluting it with aqueous buffers for experimental purposes. The most commonly reported method is extraction with 80% ethanol, followed by silica column chromatography.⁶ This method is also suitable for deriving other phenolic phytochemicals present in the sources of bakuchiol.

The first synthesis of the naturally occurring form of bakuchiol was done by Carnduff and Miller in 1967, with a Claisen rearrangement being a crucial part of the synthesis process; however, this was not enantioselective.²⁰ Other variations in chemical synthesis methods have also been developed over the years, but current methods focus on concisely synthesizing enantioselective (S)-(+)-Bakuchiol. It is also synthesized chemically in four steps from (E)-geranic acid under aldol reaction conditions, with an overall yield of 53%, increasing commercial availability.³⁰ Stock solutions of (S)-(+)-Bakuchiol synthesized from (E)-geranic acid can be made by dissolving the compound in DMSO.

However, conventional extraction methods require a large solvent volume and longer durations. Separation techniques have developed and come a long way. More sophisticated techniques, including various forms of chromatography, have been developed to extract specific compounds from the plant source.¹⁴ Other methods (supercritical fluid extraction, pressurized liquid extraction, and microwave-assisted extraction) with much shorter extraction time and lower solvent consumption may be considered for mass extraction of bakuchiol.¹⁴ They may be used on a large scale for cheaper drug development. These methods have also been used in the extractions of natural products, so their efficiency in the extraction of bakuchiol needs to be evaluated.³¹

Methods are being studied to increase the bioavailability and absorption of bakuchiol and its sources. Cho *et al.* (2011) studied the stability and physicochemical property of *P. corylifolia* extract encapsulated in 3 different vesicles (liposome, niosome, and transfersome) in nude mouse skin.³² The results of this study suggest that the use of niosome and transfersome could be a good bioavailability enhancement system (BAES) for *P. corylifolia* extract to improve skin permeation and stability, highlighting the importance of finding methods to increase the bioavailability of bakuchiol and other phenolic phytochemicals.³²

Therapeutic applications of bakuchiol

A large number of studies have evaluated the role of various phytochemicals and their pharmacological applications in communicable and non-communicable diseases.³³ In addition, other potentially beneficial compounds have also been extracted from the plant sources of bakuchiol.³¹ However, since this review focuses on bakuchiol and its pharmacological benefits, other phytochemicals and compounds will not be reviewed in detail and will only be referred to as appropriate. A brief description of the extraction and solubility of bakuchiol precedes the comprehensive analyses of its various pharmacological benefits. The mechanism of actions, functions, and uses of the naturally occurring compound bakuchiol and its implications in therapeutic approaches are described below and illustrated in [Figure 3](#).

Anti-Inflammatory effects of bakuchiol

Inflammation is generally caused by the production of pro-inflammatory mediators and cytokines such as nitric acid, prostaglandin E2 (PGE2), tumor necrosis factor-alpha (TNF- α), and interleukin 6 (IL-6).³⁴ The anti-inflammatory effects

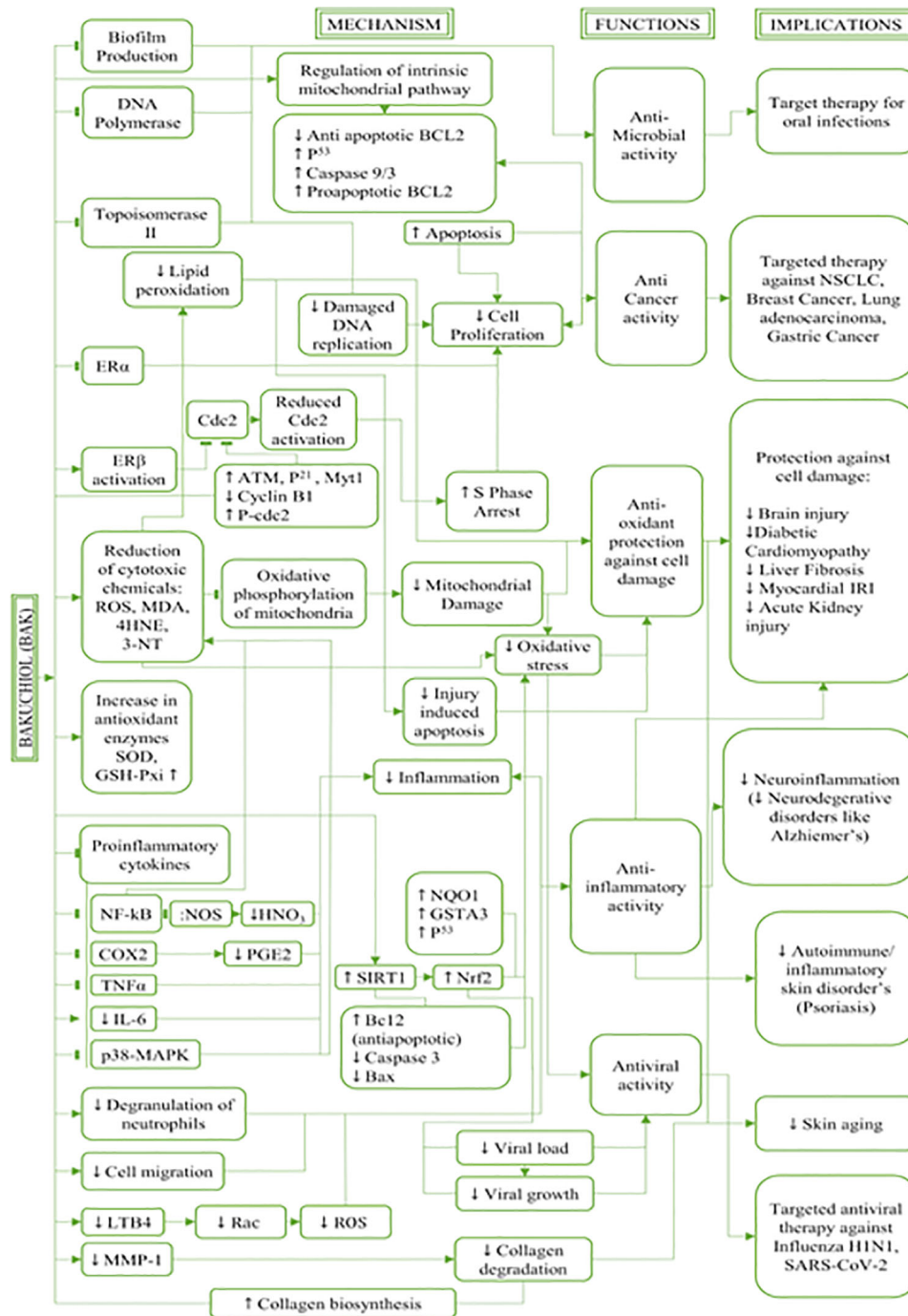


Figure 3. Mechanism of actions, functions, and uses of the naturally occurring compound bakuchiol and its implications in therapeutic approaches. This figure is an original figure produced by the author(s) for this review article.

of bakuchiol have been evaluated in multiple studies, and it has been found that the anti-inflammatory effects of bakuchiol work via various mechanisms.⁷ It can inhibit the degranulation of neutrophils and decrease cell migration and myeloperoxidase activity (involved in producing oxidants such as hypochlorous acid) in inflammatory sites, generating multiple mechanisms of controlling leukocyte function and inflammation in various types of cells.³⁵

Studies have reported the ability of bakuchiol to inhibit nitric acid and PGE2 production, both pro-inflammatory mediators generated by inducible enzymes nitric oxide synthase and cyclooxygenase-2.⁶⁻⁸ A concentration of 50µM

of bakuchiol has shown a reduction in nitric acid and PGE2 in macrophages by over 50% without exhibiting cytotoxicity.⁶ Bakuchiol can inhibit the expression of nitric acid synthase gene via the inactivation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), which can inhibit nitric acid production and IL-6 induced signal transducer and activator of transcription 3 (STAT3) activation, inhibiting IL-6 production in multiple cell lines.³⁶ This is comparable to other natural compounds, such as aurantiamide acetate from the roots of the *Baphicacanthus cusia*.³⁷

Bakuchiol can suppress inflammatory responses via downregulation of the p38 MAPK/ERK signaling pathway in microglia cells controlling neuroinflammation.⁷ Moreover, it can reduce the production of leukotriene B4 (LTB4), which contributes to disease severity in chronic inflammatory diseases in a dose-dependent manner.³⁸ LTB4 can generate reactive oxygen species (ROS) via a Rac-dependent pathway, and a reduction in LTB4 production also reduces ROS production.³⁹ Bakuchiol and its derivatives have also exhibited inhibitory activities in lipopolysaccharide (LPS) induced NO production in macrophages.⁴⁰

Bakuchiol decreases the phosphorylation of ERK, p38, and NF-κB. It arrests the mRNA expression of pro-inflammatory molecules, including TNF-α and interleukin-1β (IL-1β), and inducible nitric oxide synthases (iNOS) in Methylglyoxal-administered mice, which reduces inflammation and helps in the prevention and control of diabetes.⁴¹

Altogether, bakuchiol can provide beneficial therapeutic implications in treating inflammatory diseases such as nephritis, asthma, diabetes, skin inflammatory conditions such as psoriasis, and neurodegenerative disorders such as Alzheimer's.⁴⁰⁻⁴²

Antimicrobial effects of bakuchiol

Nature provides a great potential source for antimicrobial drug discovery. Phytochemicals extracted from natural sources are considered to have fewer side effects and a variety of functions, and some exhibit antimicrobial activity. In addition, natural compounds are much more accessible than synthetic compounds available for treatment; most developing countries depend on plant-based medications as the first line of treatment.⁴³

Terpenes such as thymol, carvacrol, eugenol, and menthol, most commonly used in fragrances and aromatherapy, show broad-spectrum antimicrobial activity through efflux pump inhibition and inhibition of bacterial growth.⁴⁴⁻⁴⁶ Bakuchiol is also a terpene that has recently been characterized to have multi-beneficiary effects on disease control, both communicable and non-communicable.

The antimicrobial effects of bakuchiol have been studied as a natural source of oral healthcare, and multiple studies have shown potent antimicrobial activity.^{11,47,48} Studies evaluating bakuchiol's antimicrobial effect have shown potent antibiotic effects against *Streptococcus aureus*. Another study examining the antimicrobial effects of bakuchiol against *Streptococcus mutans* showed increased inhibition in the growth of colonies in a dose-dependent manner. Similar results were observed for *Streptococcus sanguis*, *Streptococcus salivarius*, *Streptococcus sobrinus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Actinomyces viscosus*, *Porphyromonas gingivalis* and other bacterial strains that contribute to oral diseases.¹¹

Conventional treatments for oral infections usually contain chlorhexidine, a gold standard.⁴⁹ However, as it was toxic in large quantities and caused discoloration of the tooth surface, other natural-based alternatives were evaluated, some of which were successful inhibitors for antimicrobial growth.⁵⁰⁻⁵³ There is also a concern about emerging antimicrobial resistance, which has increased rapidly in the past decade and is now one of the leading causes of death.^{54,55} Given the increasing emergence of antimicrobial drug-resistant strains, finding nature-based alternatives to antibiotics is vital to help control the resistance.

Bakuchiol works by rupturing the cell membrane in bacterial strains, inhibiting DNA polymerase and other DNA replication enzymes, and reducing biofilm production by *E. faecalis* and *E. faecium*.⁵⁶ These studies implicate the potential uses of bakuchiol in maintaining oral health care. It can potentially be used in combination with other natural pre-existing methods of oral healthcare to target the increasing demand in the market for natural healthcare products.

Bakuchiol also has antifungal effects, and ethanol isolates of bakuchiol from PF effectively inhibit the growth of dermatophytes *in vitro*.⁵⁷ Oral *Candida* species have also been susceptible to bakuchiol treatment with minimum inhibitory concentration (MIC) ranging from 12.5 to 100 µg/mL, causing a reduction in growth rates, viable counts, cell metabolic activity and biofilm mass.⁵⁸

Bakuchiol in the treatment of skin disorders

Bakuchiol has recently gained mass popularity as an active component in skin care products due to its functional similarity with retinoid compounds and relatively higher tolerability.⁵⁹ It has been shown to work with melatonin and vitamin C derivatives to regulate genes involved in the modulation of angiogenesis, collagen biosynthesis, skin barrier function, and other aspects of skin cell biology.⁹ Bakuchiol also has retinol-like properties in modulating genes that regulate extracellular matrix production and the dermal-epidermal junction.⁶⁰ It can help deter skin aging by enhancing human fibroblast cell activity and inhibiting the expression of matrix metalloproteinases by increasing tissue inhibitors of metalloproteinases-1 (TIMP-1), tissue inhibitors of metalloproteinases-2 (TIMP-2), collagen type I (Col I), and collagen type III (Col III) mRNA, and decreasing the expression of matrix metalloproteinase-1 (MMP-1) mRNA.⁶¹

Bakuchiol exhibits retinol-like functionality causing upregulation of types I, III, and IV collagen, which make up the skin's extracellular matrix and basement membrane, in *in vitro* models.⁴ When formulated into a skincare product, regularly applied, and tested under clinical settings for 12 weeks, significant improvement in facial fine lines and wrinkles were observed, along with improvements in skin elasticity, firmness, and pigmentation, as well as a reduction in photodamage.⁴ This effect was observed in multiple studies on participants of varying races.^{4,59} In addition, other studies have also confirmed an increase in moisture retention from the regular application of products formulated with bakuchiol extract.⁶² It also works synergistically with other natural compounds to reduce inflammation and protect and maintain naturally aging skin.¹⁰

This higher tolerability allows bakuchiol to be an effective anti-aging treatment for people of all skin types. Furthermore, it can also be formulated for people with hyperpigmentation historically perceived as less tolerant of retinol.⁶³

Unlike retinoids, bakuchiol can be used daily due to its photostability.⁵⁹ Combinations of retinoid and bakuchiol therapy also reduce oxidative stress induced by retinoids,⁶⁴ as bakuchiol helps to stabilize retinol under photo-oxidative environments.

Bakuchiol works as an antioxidative agent due to its ability to interfere with free radical production, decrease the translocation of mitochondrial apoptosis-inducing factors, and its ability to quench superoxides and other radicals *in vitro*.^{13,49} Overall, it can be deduced that its naturally occurring phytochemical functions as a potent antioxidant that can help maintain cellular turnover and ensure protective functions for all organs. With higher tolerability, photostability, and ability to slow down skin aging, bakuchiol can be considered a suitable plant-based alternative to retinol, traditionally extracted from animal sources.

Antitumorigenic effects of Bakuchiol and Hormone replacement therapy

Bakuchiol has traditionally been used in medicine for the treatment of various cancers. Early studies have shown that bakuchiol can inhibit cell proliferation, and further studies have recently evaluated its mechanisms of action in various cancer cell lines compared to its analogue resveratrol.¹² It can induce ROS-related apoptosis in lung adenocarcinoma A549 cell line, S phase arrest, caspase 9/3 activation, p53 up-regulation, and B-cell lymphoma 2 (Bcl-2) downregulation, all of which contribute to anticancer activities.¹² Bakuchiol has also shown inhibitory effects on DNA polymerase enzymes, while a related compound Bakuchicin inhibits the actions of topoisomerase II.⁶⁵ Its effects on DNA replication enzymes and relatively much lower cytotoxic effects than its analogue resveratrol make it a potent tolerable therapeutic compound for treating non-small cell lung cancer.¹²

High doses of Bakuchiol (>2 µg/mL) inhibited cell proliferation of breast cancer MCF-7 cells through actions via estrogen receptors (ER), inducing ERβ expression and suppressing ERα expression.⁶⁶ S phase arrest was also observed in MCF-7 cells along with upregulation of ATM serine/threonine kinase (ATM), phosphorylated cell division cycle protein 2 (P-Cdc2), p21, myelin transcription factor 1 (Myt1), and downregulation of Cyclin B1, which implies the blocking of Cdc2 activation by upregulation of ERβ may play a role in the S phase arrest.⁶⁶ It also induced apoptosis in MCF-7 cells with an increase in expression of pro-apoptotic Bcl-2 and cleaved caspase proteins, pointing towards its involvement in apoptosis via the intrinsic mitochondrial pathway, similar to that observed in the lung adenocarcinoma A549 cell line and even liver cancer cell lines.^{12,66}

In addition, bakuchiol was found to effectively inhibit the activation of hypoxia-inducible factor 1 (HIF-1) and NFκB in gastric cancer AGS and cervical adenocarcinoma HeLa cell lines.⁶⁷ It also inhibits proliferation, migration and invasion of androgen-independent prostate cancer cell line PC-3 by inactivating NF-κB signaling via Androgen receptor (AR) and ERβ expression in a time and dose-dependent manner. Bakuchiol's cytotoxicity was considered in this assay via LDH assay, and the non-toxic concentration used in further experimentation was determined to be at 10µM.⁶⁸

Bakuchiol-treated NUGC3 gastric cancer cells have also been shown to express reduced levels of phosphorylated protein kinase B (AKT) protein and increased p-extracellular signal-related kinase 1/2 (ERK1/2) and p-c-Jun N-terminal kinase (JNK) expression, indicating the induction of cell death was mitochondria-dependent, working via the MAPK/PI3K/AKT pathways.⁶⁹

Furthermore, bakuchiol was shown to induce estrogenic activity *in vivo* and *in vitro* study models.⁶⁶ It activates the ER β receptor and suppresses the ER α receptor, which reduces CDC2 activity and promotes S phase arrest, reducing tumor cell proliferation.⁶⁶ This promotes bakuchiol as a phytoestrogen and anticancer drug, promoting safer hormone replacement therapeutics. Bakuchiol can also prevent bone loss and delay osteoporosis in post-menopausal women by activating the ERs.⁷⁰ This is of increased significance as hormone replacement therapies usually use estrogen, which is linked with an increased risk of breast cancer.

There have also been other compounds extracted from *Psoralea corylifolia L.* that express similar pharmacological activities.⁷¹ Psoralidin, a natural phenolic coumarin, is one such compound that is beneficial in various diseases, including osteoporosis and hormonal cancers.⁷² This is elucidated by inducing oxidative stress and apoptosis in tumorigenic cells, which promote autophagy-dependent cell death and activate the ER signaling pathway. The use of bakuchiol or other anticancer natural compounds should be evaluated to further check their efficacy in preventing or controlling cancer development. This would provide a suitable cheaper alternative to current cancer chemotherapeutics in the market, which are not accessible equitably among patients due to high costs.

Antioxidative effects of bakuchiol

There has been an increasing interest in identifying and characterizing antioxidant compounds to treat oxidative stress and related diseases, among which bakuchiol has been characterized as it has shown vital antioxidant activities in multiple studies.^{5,20,73} When studying the scavenging activity of bakuchiol against various oxidizing radicals, it was determined that the terpenoid chains present in bakuchiol play a role in preventing lipid peroxidation.¹³ It can protect against rat liver injury by inhibiting lipid peroxidation,⁷⁴ with similar effects expressed by studies on other natural products such as pumpkin seeds and acanthoic acid.⁷⁵ Bakuchiol can also inhibit liver fibrosis and show hepatoprotective effects by inhibiting oxidative stress while inducing apoptosis in myofibroblasts, relieving the hepatotoxicity of various toxicants.^{74,76} Bakuchiol reduced cell death in retinal ganglion cells (RGC-5) and reduced ROS-induced apoptosis and cell death *in vitro*.⁴⁹

In vivo studies have demonstrated that bakuchiol reduces retinal degeneration following optic nerve injury.⁴⁹ It has also been observed that bakuchiol can protect against sepsis and sepsis-induced acute kidney injury by significantly reducing inflammation and renal oxidative stress while inhibiting induced activation of NF κ B and p38-MAPK signaling pathways in the kidneys.⁷⁷ Its ability to block NF κ B signaling also allows for cardioprotective functions, as seen in various mice models, allowing its application as a potential treatment for pathological cardiac hypertrophy.⁷⁸

In another study, bakuchiol showed protective effects against early brain injury by reducing ROS, malondialdehyde (MDA), 4-Hydroxynonenal (4-HNE), 3-Nitrotyrosine (3-NT), and other biomarkers of oxidative stress produced by lipid peroxidation.⁷⁹ Conversely, it causes increases in the enzyme activity of superoxide dismutase (SOD) and inducible glutathione peroxidase (GSH-Pxi), both of which play crucial roles in the body's antioxidant defense system while reducing mitochondrial damage. As seen in this study, phosphorylation of AMP-activated protein kinase (AMPK) and thioredoxin 1 (Trx1) protein levels increased. In contrast, thioredoxin-interacting protein (TXNIP) levels decreased due to treatment with bakuchiol, which was thought to have occurred due to the regulation of Trx1 and TXNIP levels.

Bakuchiol may be considered a potential candidate for the prevention and treatment of insulin resistance as it can reduce induced insulin resistance and oxidative stress with reduced ROS expression and enhanced antioxidant enzyme expression.⁴¹

Bakuchiol can also reduce the severity of myocardial ischemia-reperfusion injury (IRI) by impairing mitochondrial oxidative damage through regulation of sirtuin 1/proliferator-activated receptor gamma coactivator 1-alpha (SIRT1/PGC-1 α) pathway signaling via increased in the expression of SIRT1.⁸⁰ It reduced mitochondrial oxidative damage by increasing the action of mitochondrial succinate dehydrogenase, cytochrome c oxidase, and mitochondrial SOD and decreased the production of malondialdehyde.⁷⁹

Bakuchiol has also increased anti-apoptotic Bcl2 and decreased pro-apoptotic Bax and cleaved caspase 3, which helps control injury-induced cell death, and inhibitors of SIRT1 abolished the effects of bakuchiol further highlight the role of

its interaction with SIRT1 signaling.⁷⁸ Bakuchiol has also been found to reduce hyperglycemia-induced cardiomyopathy by activating the SIRT1/Nrf2 pathway, which reduces myocardial oxidative stress and elevates antioxidant production.⁷³

Similar effects are observed in other natural products such as curcumin, melatonin, berberine, and icariin.^{80–84} These also reduce myocardial IRI via other pathways, highlighting the importance of studying the other potential signaling pathways regulated by bakuchiol, which leads to its ability to reduce injury-induced cell damage. Moreover, bakuchiol should be combined with other natural compounds with similar protective effects for potential synergistic activity.

Antiviral effects of bakuchiol

The antiviral effect of bakuchiol has been evaluated in some studies.^{15,85,86} Viral diseases are constantly evolving in pathogenicity, and certain strains have been reported to be highly pathogenic to humans, as was seen in the influenza A pandemic in 1918, causing 50 million deaths,⁸⁷ and in the current pandemic caused by the SARS-CoV-2 virus,⁸⁸ which has infected more than 500 million people and has caused more than 6 million deaths since its first reported case on Dec. 31, 2019.⁸⁹ The SARS-CoV-2 virus enters the host cell via the interaction between its receptor-binding domain (RBD) of spike glycoprotein with the angiotensin-converting enzyme 2 (ACE2) receptor found on the plasma membrane of the host cell.⁹⁰ Given the rapid emergence of resistant viral strains, searching for potent and tolerable antiviral drugs is essential to combat and control viral infections.

Plant-based natural compounds are being examined extensively for their therapeutic effects,^{91,92} and bakuchiol has also been evaluated, given its use in traditional medicine systems to treat a wide range of diseases. In *in vitro* studies on Madin-Darby canine kidney (MDCK) cells infected with influenza A H1N1 strain, the naturally occurring form of bakuchiol was found to inhibit influenza A growth and infection while reducing expression of viral mRNAs and proteins, decreasing viral load.¹⁵ In addition, it also was able to activate Nrf2 and two Nrf2-induced genes, NAD(P)H quinone oxidoreductase 1 and glutathione S-transferase A3, promoting activation of transcriptional regulation and regulating virus-induced host body oxidative stress response. To a lesser extent, these effects were also observed in its enantiomer form, highlighting the importance of chirality in designing potent antiviral drugs.

Further studies on related compounds such as cyclobakuchiols A, B, and C, derived from (+)-(S)-Bakuchiol as well as from its natural sources, have also established strong potential to inhibit viral growth, infection, and expression of viral mRNAs and proteins in influenza A virus-infected MDCK cells via similar mechanisms.⁸⁵ Other natural compounds derived from natural sources show antiviral actions against Influenza A, such as aurantiamide acetate extracted from the plant's roots *Baphicacanthus cusia*.³⁷ These compounds work via similar mechanisms as bakuchiol, as observed in MDCK cells. In addition, these natural compounds also reduce virus-induced inflammatory responses via the suppression of NF-κB signaling pathways and pro-inflammatory cytokines.⁹³

In a more recent study, bakuchiol effectively inhibited severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pseudovirus entry at concentrations of up to 100 μM without toxicity. Furthermore, in HEK293 cell lines overexpressing human ACE2 receptors, bakuchiol also effectively blocked RBD-ACE2 binding at the cell membrane.⁸⁶ This also implies that further evaluation of bakuchiol on its effect on other viral diseases is critical in the current pandemic setting caused by the SARS-CoV-2 virus to find effective antiviral treatments to reduce disease transmission and severity.

Other natural compounds have also been evaluated in recent studies, among which epigallocatechin gallate (EGCG), 20(S)-ginsenoside Rg3 (SRg3), 20(R)-ginsenoside Rg3 (RRg3), isobavachalcone (Ibvc), and isochlorogenic A (IscA) were found to effectively inhibited pseudovirus entry at concentrations up to 100 μM.^{86,94}

Among these compounds, EGCG and Ibvc have shown comparable effects to bakuchiol administration by inhibiting the SARS-CoV-2-induced cytopathic effect and plaque formation and demonstrating a dual binding to RBD and ACE2.⁹³ Another compound, 1,2,3,4,6-O-Pentagalloylglucose (PGG), also effectively inhibited virus binding and infection in ACE2 overexpressing human host cells, binding more with Spike-RBD than ACE2 receptors.⁹⁵ It blocks the fusion of SARS-CoV-2 to hACE2 receptors on a dose-dependent level. Spike RBD PGG was also found to exhibit anti-influenza-virus activity by reducing the accumulation of nucleoprotein and viral hemagglutinin in plasma membranes at the late stage of the replication cycle and inhibiting the release of progeny virus from infected cells. PGG also works in ameliorating HBV, HCV, HIV infections.⁹⁵ PGG may be a safe and potential antiviral agent against COVID-19 by blocking the fusion of SARS-CoV-2 spike-RBD.

Combination effects

Most studies evaluating the effects of bakuchiol used in combination with other molecules tend to be formulated by the cosmeceutical industry. It is also used in combination with retinol to help increase its photostability, or moisturizing molecules like squalene, working synergistically to improve skin elasticity and texture.

Bakuchiol can be combined with *Vanilla tahitensis* extract to inhibit skin photoaging and cause improvement in skin barrier function and elasticity, increasing cellular turnover and improving signs of aging.¹⁰ A study by Bacqueville *et al.* used an *in vitro* skin model made of human dermal fibroblasts treated with the compounds alone or in combination, after which they were exposed to an acute dose of UVA. Exposure to UVA-induced significant morphological changes and increased IL-8 and p16 expression in the control model (no treatment), suggesting inflammation and senescence. Compared to control, treatment with either compound alone prevented actin network alteration and IL-8 upregulation, while protecting against IL-8 and p16 overexpression in combination. This combination was also formulated into serum and tested in participants who applied it twice daily for 56 days. These compounds can work synergistically to reduce ptosis and skin deformation and improve the radiance of naturally aged skin in women.

A face serum containing bakuchiol, palmitoyl tripeptide-38, hydrolyzed hyaluronic acid and a polyherbal and vitamin blend was tested in 55 healthy adults. Daily use for 3 months indicated improvements in skin as seen in *in vitro* studies and clinical trials on healthy volunteers.⁶⁰ Protection of skin structure was observed *in vitro* with reduced collagenase activity and significant free radical scavenging activity as observed through increased gene expression of dermal collagen, elastin and hyaluronic acid synthesis. In addition, substantial improvements in skin elasticity, hydration, roughness (fine lines and wrinkles), and brightness occurred during the trial.

It also works marvelously in combination with melatonin and ascorbyl tetraisopalmitate to cause significant clinical anti-aging effects when applied once daily,⁹⁶ with a statistically significant decrease in wrinkles and redness, an increase in skin firmness and overall improvement in skin quality and complexion as well as hydration.⁹⁶ A combination of bakuchiol, Ginkgo biloba extract and mannitol was also shown to improve the efficacy of adapalene treatment in patients suffering from Acne Vulgaris.⁹ It has also been found to work exceptionally well with salicylic acid in managing P. acnes.⁹⁷

Outside of the dermatocosmetic industry, the use of bakuchiol can also improve the efficacy of various non-cosmetic treatments. Bakuchiol has been found to work in combination with tumor necrosis factor (TNF)- related apoptosis-inducing ligand (TRAIL) to inhibit the growth of TRAIL sensitive (HCT116) and resistant (HT-29) colon cancer cell lines.⁹⁸ Combination treatment of bakuchiol with TRAIL on these cell lines significantly upregulated the expression of TRAIL cell death receptors DR4 and DR5 in a dose-dependent manner, as well as the expression of the pro-apoptotic proteins PARP and the cleaved caspases 3, 8 and 9, while suppressing the expression of survival proteins such as cFLIP, survivin, XIAP and Bcl2. Pretreatment of cells with JNK inhibitor SP600125 and ROS scavenger N-acetylcysteine and the depletion of DR4 or DR5 by **small interfering RNA** reduced the bakuchiol-induced cell growth inhibition. Bakuchiol assists with TRAIL-induced apoptosis via the ROS/JNK pathway.

When used alone or in combination with *Allium sativum*, it also demonstrated potent antimicrobial properties, with bakuchiol and *Allium sativum* showing synergistic effects when used in combination.⁹⁹

Side effects

Bakuchiol is generally used in the cosmeceutical field as a more tolerable version of retinol, having retinol functionality through retinol-like regulation of gene expression. However, it may initially cause some redness and peeling in sensitive skin,⁴ although chances are rare due to the established anti-inflammatory nature of bakuchiol. As it may increase cellular turnover, sunscreen is recommended for use after applying bakuchiol-containing products to reduce damage by UV radiation. Retinol and its derivatives are generally discouraged for use during pregnancy. No studies have been done to evaluate use safety in pregnant women, so use should be carefully conducted. It is difficult to quantify the benefits and side effects of bakuchiol usage as most studies have been done *in vitro*, potentially introducing a risk of bias.

It should be mentioned that studies have found bakuchiol to be non-toxic to cell cultures even in high concentrations of up to 5000 uG/mL,¹⁰⁰ however, this was only observed in *in vitro* studies, and further studies are required to determine dosage toxicity. Recent clinical reports have indicated that treatment with *Psoraleae Fructus* (PF), an essential source of Bakuchiol, is associated with an increased risk of liver injury.^{25,26,100–104} A study by Guo *et al.* (2021) indicated that bakuchiol, among other constituents of *Psoraleae Fructus* induced oxidative stress and mitochondrial damage-mediated apoptosis, alleviated when Ethanol extracts of PF were used. Bakuchiol may induce cholestatic hepatotoxicity as treatment with Bakuchiol reduces mRNA expression of CYP7A1, HMG-CoA reductase, PPAR α , and SREBP-2.¹⁰⁵

Care should be taken when using bakuchiol in combination therapy because it may cause an increase in cytotoxic effects of bakuchiol, and extensive studies should be conducted to ensure that metabolic toxicity does not occur. Bakuchiol can induce nephrotoxicity when it is used in combination with other natural ingredients such as Glycyrrhetic acid (GA) found in licorice, which inhibits the CYP450 isoenzymes (CYP3A4, CYP2C9, CYP1A2) involved in metabolic detoxification of bakuchiol.¹⁰⁶ The presence of GA altered the toxicokinetics of bakuchiol in rats, increased the internal exposure, suppressed the elimination of the bakuchiol prototype, and therefore may have enhanced the renal nephrotoxicity.

Conclusions

This review focused on the pharmacological benefits of the compound bakuchiol, traditionally isolated from the bakuchi plant and used in traditional medicine for centuries. Recent studies have highlighted its vital role in controlling several activities that lead to health depreciation and the onset of various non-communicable diseases. Additionally, bakuchiol has shown potent antimicrobial and antiviral responses against various pathogens in multiple studies, which allows for the development of potential novel cures and preventive strategies.

Moreover, extensive research is required on the non-toxic extraction of the compounds, fully realizing its pharmacological and biochemical modes of action, and planning for sustainable ways of growing its sources to meet the increasing demands of the pharmaceutical industries. Further studies should also be done to evaluate the long-term effects of prolonged bakuchiol consumption, possibly via retrospective analyses, which have not been done yet.

Data availability

No data are associated with this article.

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Reviewer Report 31 August 2023

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Naoufal El Hachlafi 

Universite Sidi Mohamed Ben Abdallah, Fes, Fes-Boulemane, Morocco

The manuscript entitled: "Bakuchiol and its pharmacological benefits", presents interesting and valuable work, which is within the scope of the journal F1000Research. It is well-written. However, some minor corrections are needed to make this paper accepted for indexing. I encourage the authors to consider making the necessary changes.

General Considerations

The authors should carefully proof-read the entire manuscript to minimize typographical errors, especially with spellings, punctuation, unnecessary capitalizations, spaces, and units, as well as to ensure uniform expression of various special characters and abbreviations, terms, and phrases.

Results and discussion

The description of the results is clear; however, it would be helpful to provide more details in tables taken into account different *in vitro* and *in vivo* clinical studies carried out in this subject.

Conclusion

Conclusion should be improved by adding concluding remarks and future direction for further investigation in the field.

References

Ensure all references are relevant and up-to-date. It's essential to cite the most recent and pertinent research in the field to demonstrate a sound understanding of the current state of knowledge.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacology, essential oils, bioactive compounds, antimicrobial, antioxidant

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 June 2023

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Amit Baran Sharangi 

Department of Plantation Spices Medicinal and Aromatic Crops, Bidhan Chandra Krishi Viswa Vidyalaya, Nadia, West Bengal, India

The article entitled "Bakuchiol and its pharmacological benefits" by Nizam et al., is a routine exercise wherein a systematic review approach summarized, analyzed, interpreted and concluded about the therapeutical values of the compound "bachuchiol" from the leaves and seeds of *Psoralea corylifolia* medicinal plants. While the potential of the same is pharmacologically great, the following are some of my observations on the article which needs immediate attention by the authors and rigorous revision before indexing:

1. To apprise the readers about the origin of the compound "Bakuchiol".....ie., whether it is synthetic or natural (plant based).....some appropriate words may be given in the title itself:
-it may be like Bakuchiol from *Psoralea corylifolia* L.
-it may be like Natural bakuchiol, etc

The above is for clarity in understanding only.

2. In the "Introduction", placement of Ref 17 is probably at a wrong position.
3. In the "Results", in the first subhead, the word 'material' has been repeated. Here, the last sentence may be separated into two.
4. Therapeutic applications of bakuchiol: This portion seriously lacks in one or two summarized table containing some global research-based interesting information on In vivo

Test, In vitro Test, Plant parts used, Visible / projected Effects, Model used(if any), References, etc

5. Just before "Side effects", was it necessary to hyperlink the highlighted words?
6. After "Side effects", some discussion was necessary on the Phytochemical screening and toxicity study of this very medicinal plants or the compound bakuchiol derived from itin a different subtitle along with contraindication, if any and of course, supplemented with a well organised table with convincing references was necessary [LD50 (mg/kg), Phytochemical constituents, References in the last column of the table].
7. Instead of Conclusion, it may be replaced with Conclusion and Future research. In that case, there should be some restructuring of the text with inclusion of some promising upcoming areas of futuristic research in this direction.

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Herbs, spices, medicinal and aromatic crops

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 31 Oct 2023

Md. Kamrul Hasan

The article entitled "Bakuchiol and its pharmacological benefits" by Nizam et al., is a routine exercise wherein a systematic review approach summarized, analyzed, interpreted and concluded about the therapeutical values of the compound "bachuchiol" from the leaves and seeds of *Psoralea corylifolia* medicinal plants. While the potential of the same is pharmacologically great, the following are some of my observations on the article which needs immediate attention by the authors and rigorous revision before indexing:

To apprise the readers about the origin of the compound "Bakuchiol".....ie., whether it is synthetic or natural (plant based).....some appropriate words may be given in the title itself:

-it may be like Bakuchiol from *Psoralea corylifolia* L.

-it may be like Natural bakuchiol, etc.

Authors' response: Thank you. The revised version addressed this issue and fixed.

The above is for clarity in understanding only.

In the "Introduction", placement of Ref 17 is probably at a wrong position.

Authors' response: Addressed and fixed. Thank you.

In the "Results", in the first subhead, the word 'material' has been repeated. Here, the last sentence may be separated into two.

Authors' response: Thank you. Addressed and fixed.

Therapeutic applications of bakuchiol: This portion seriously lacks in one or two summarized table containing some global research-based interesting information on In vivo Test, In vitro Test, Plant parts used, Visible / projected Effects, Model used(if any), References, etc.

Authors' response: Thank you so much for the suggestion. The authors revised the manuscript as suggested.

Just before "Side effects", was it necessary to hyperlink the highlighted words?

Authors' response: Thank you. Hyperlink removed.

After "Side effects", some discussion was necessary on the Phytochemical screening and toxicity study of this very medicinal plants or the compound bakuchiol derived from itin a different subtitle along with contraindication, if any and of course, supplemented with a well organised table with convincing references was necessary [LD50 (mg/kg), Phytochemical constituents, References in the last column of the table].

Authors' response: Thank you so much. The authors revised the manuscript by adding a table as suggested.

Instead of Conclusion, it may be replaced with Conclusion and Future research. In that case, there should be some restructuring of the text with inclusion of some promising upcoming areas of futuristic research in this direction.

Authors' response: Thank you. Addressed and revised.

Competing Interests: No competing interests were disclosed.

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