Unravelling the Molecular Mechanisms: an Updated Review on the Pharmacological Targets of Bryophyllum Pinnatum

Aditya A. Gadekar[#1], Swati U. Kolhe[*2], Sakshi R. Lonkar[#3]

Pharmacology Department, Savitribai Phule University

[1]nameadityta123@gmail.com

[2]sakshilonkar610@gmail.com

[3]Kolhe_su@aissmscop.com

Abstract- **Bryophyllum pinnatum Oken is a succulent plant from the Crassulaceae family used as a medicine for wounds, inflammation, ulcers, and metabolic diseases. The biological activity of this plant is mainly associated with secondary metabolites such as bufadienolides, flavonoid glycosides, triterpenes, and phenolic acids. Modern research has proven that these phytochemicals can affect the molecular pathways involved in the development of cancer, diabetes, and viral infections, although their clinical applications are still limited. Standardized preparations of B. pinnatum have been used as a tocolytic agent in Switzerland for decades, proving that some of its applications are already beyond the preclinical level. The phytochemicals of B. pinnatum can influence cancer cell activity, affecting apoptosis, angiogenesis, and metastasis through the PI3K/AKT, MAPK, Wnt/β-catenin, and Nrf2 signaling pathways. Moreover, leaf extracts of this plant were shown to recover barrier functions in colitis models due to a decrease in TLR4 and NF-κB p65 expressions. The ethanolic extracts demonstrated cytotoxic effects on HT-29 colon cancer cells. Docking and bioactivity experiments in metabolic research have shown that luteolin, friedelin, isorhamnetin-3-O-rutinoside, quercetin, kaempferol, and other compounds may act as inhibitors of aldose reductase, α-amylase, and α-glucosidase. Further in silico investigations have found that rutin, astragalin, and luteolin can bind to the SARS-CoV-2 main protease and spike protein. Although these results seem promising, safety poses a challenge. According to recent clinical studies and a case study from 2025, leaf consumption is associated with systemic toxicity and death. This highlights the cardiotoxicity of bufadienolides, which are similar to digoxin and act as Na+/K+-ATPase inhibitors.**

Keywords- Bryophyllum pinnatum; Bufadienolides; Molecular Docking; PI3K/AKT/NF-κB Signaling; Phytopharmacology

I. INTRODUCTION

Bryophyllum pinnatum Oken, also known as Kalanchoe pinnata Pers., belongs to the family Crassulaceae [1]. This succulent plant originally comes from Madagascar but is now found in parts of Africa, Asia, Latin America, and India [2].The plant has many names, including "life plant," "wonder leaf," "cathedral bells," and "air plant" in Europe and the Americas, "saião" or "coirama" in Brazil, and "da bus i" in Yunnan Province, China, among others. In studies on traditional uses, the plant has been used in a wide range of ways, such as applying it externally to treat wounds, burns, boils, and abscesses, or using its leaves in infusions and decoctions for stomach and duodenal ulcers, jaundice, hepatitis, and respiratory infections. It is also used for treating coughs, asthma, and fever [3], [4]. In some regions, the leaves are used for kidney stones, high blood pressure, and diabetes, while the plant is also used in Trinidad, Madagascar, and Nigeria for treating rheumatism, leishmaniasis, and snakebite [3], [5].

The chemical make-up of B. pinnatum includes four major types of plant chemicals. One of these is a unique group called bufadienolides, which are a kind of cardiac glycoside [6]. These have been found in this plant and related species, with thirteen different types reported [7].The main ones, such as bryophyllin A, B, and C, as well as bersaldegenin derivatives, have been measured in the leaves using a technique called ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) [8]. The total amount of these chemicals in the leaves ranges from 3.78 to 40.50 mg per 100 grams of dry weight, and younger leaves tend to have more of these compounds [1], [5].The second group consists mainly of flavonoids, like quercetin and kaempferol glycosides, and some derivatives of luteolin, acacetin, and diosmetin [1], [5], [9].

Besides these, the plant also contains triterpenes such as friedelin and β-amyrin acetate, sterols like stigmasterol and campesterol, phenolic acids including gallic, caffeic, and coumaric acids, phenanthrene derivatives, and organic acids such as L-malic and citric acid [1], [5]. These compounds are usually isolated by soaking the plant material in a mixture of water and ethanol or methanol, and are analyzed using high-performance liquid chromatography with diode-array detection, nuclear magnetic resonance, and ultra-performance liquid chromatography coupled with photodiode-array detection and electrospray ionization quadrupole time-of-flight tandem mass spectrometry (UPLC-PDA-ESI-QTOF-MS/MS) [1], [5]. Preclinical and clinical studies have shown that B. pinnatum has a wide range of medicinal benefits. Extracts from the leaves, such as ethanolic, chloroform, and aqueous, have been found to kill cancer cells in the lab, including cancer cells from the cervix (HeLa), colon (HCT116), and pancreas (BxPC-3 and PANC-1). These extracts caused cell death, especially in the case of colon cancer, where it led to 49.5% cell death by triggering p53-dependent apoptosis. In animal models of colitis, a hydroethanolic extract at doses of 100 and 200 mg/kg helped reduce colon shortening, lowered inflammation markers, and reduced levels of certain inflammatory proteins. A topical gel made from the plant has also been shown to help with wound healing by reducing the size of wounds and lowering inflammation while increasing vascular endothelial growth factor. The plant has also been proven to inhibit enzymes linked to high blood sugar, and has been used to reduce preterm births in Switzerland, with a significant drop in preterm delivery rates after its use in obstetric protocols [5].

Research into the mechanisms of action has grown considerably in the last five years. Studies have now begun to identify some of the proteins and signaling pathways involved in the plant's medicinal effects [10]. Gallic acid, caffeic acid, coumaric acid, and quercetin have been found to inhibit the PI3K/AKT/mTOR signaling pathway, which is involved in some cancer models. This pathway also interacts with BCL-2 and p53, as well as the FoxO/GSK-3β signaling cascade[1]. Some flavonoids have been shown to block the movement of β-catenin, which is linked to the Wnt/β-catenin pathway. Stigmasterol and isorhamnetin-3-O-methylquercetin have also been found to stop cancer cell migration and invasion by affecting matrix metalloproteinase levels. Quercetin also stops the activation of certain protein pathways in cancer models and can increase the effectiveness of other cancer treatments like cisplatin. The NF-E2-related factor 2 pathway is thought to be connected to the antioxidant properties of phenolic compounds and may also play a role in wound healing by boosting vascular endothelial growth factor production [5].

Network pharmacology and molecular docking studies have identified key biological targets and pathways that B. pinnatum's chemical components interact with. These include dipeptidyl peptidase-4 and α-amylase/α-glucosidase in type 2 diabetes. In one study, over 180 chemical compounds were evaluated against DPP-4, with molecular docking scores between -2.941 and -5.623 kcal/mol, and the stability of the interactions was confirmed through molecular dynamics simulations lasting 150-200 nanoseconds. Other in silico studies have shown that bryotoxin B binds to the spike protein of SARS-CoV-2 at -9.9 kcal/mol, β-amyrin acetate docks at -9.5 kcal/mol, and 3,6-diglucosylapigenin inhibits the 3C-like protease at -10.59 kJ/mol, with activity confirmed at 125.5 µg/mL. However, these predictions still need to be tested in real-life conditions [7]. Additionally, the compound bryophyllin B has been found to strongly interact with interleukin-6, suggesting it could help manage the cytokine storm seen in severe cases of coronavirus disease 2019 [11].

A number of reviews published between 2019 and 2026 have compiled information on the chemical makeup, medical uses, and traditional applications of B. pinnatum. However, the current body of research is limited by several factors. The understanding of the plant’s molecular mechanisms is not fully integrated and is spread out across studies focused on different diseases. Rapidly increasing in silico data and information related to SARS-CoV-2 and antiviral properties have not been thoroughly discussed. Evidence from network pharmacology and molecular docking has also been presented in separate studies, and there is still more work to be done to fully understand the role of this plant in various health conditions.

The review includes primary peer-reviewed studies, authoritative reviews and registered clinical data published up to May 2026 and obtained from PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, SpringerLink and Google Scholar as well as through manual reference-list screening of seminal papers. Study designs included in vitro cell-based assays, in vivo rodent models, ex vivo organ bath experiments, in silico molecular-docking and molecular-dynamics simulations and clinical investigations, such as retrospective cohort analysis, matched-pair studies and registration trials. On the contrary, only agronomics and purely analytical methodology articles are accepted for support, with in vivo validation of recent docking claims of antiviral agents as a future priority.

II. BOTANICAL DESCRIPTION AND DISTRIBUTION

A. Taxonomy and Morphology

Bryophyllum pinnatum Oken is a perennial, succulent herb classified under the order Rosales, family Crassulaceae, and subfamily Kalanchoideae. Its hierarchical taxonomy situates the species within the kingdom Plantae; subkingdom Tracheobionta; division Magnoliophyta; class Magnoliopsida; subclass Rosidae; order Rosales; family Crassulaceae; genus Bryophyllum; and species B. pinnatum. The genus Bryophyllum encompasses approximately 25 succulent, perennial taxa indigenous to Madagascar. Certain investigators regard this genus as one of three distinct subgroups — Kitchingia, Bryophyllum, and Eukalanchoe — subsumed within the broader genus Kalanchoe [1]. The accepted binomial in global taxonomic repositories is Bryophyllum pinnatum, originally circumscribed by Lamarck under the basionym Cotyledon pinnata, with widely recognized heterotypic synonyms including Kalanchoe pinnata Pers., Bryophyllum calycinum Salisb., and Crassula pinnata. More than 20 nomenclatural synonyms have been documented [1]. Depending on edaphic and climatic parameters, the plant attains a height of 30–120 cm, occasionally exceeding 1.5 m [8], [12].

The aerial portions of the plant are glabrous, with quadrangular, hollow, and fleshy stems characteristic of the family. Juvenile specimens bore stems with reddish mottling on a whitish background, whereas mature specimens displayed uniformly pale-green stems. The foliage is decussate, measuring approximately 10–20 cm in length, and presents as either simple or pinnately compound with three to seven leaflets on the upper internodes. Each leaf is articulated to a ridge encircling the stem and exhibits a thick, coriaceous, and dark-green lamina, a feature archetypal of Crassulaceae. Adventitious plantlets arising from marginal crenations confer the vernacular designation "mother of thousands" and exemplify a hallmark reproductive trait of the family, along with its capacity for crassulacean acid metabolism [12], [13]. The inflorescence is a terminal panicle bearing pendulous, tubular corollas of 5–7 cm in length, with hues ranging from pale greenish-yellow to deep reddish-purple. Indehiscent follicular fruits persist on plants at maturity. Within Crassulaceae, the capacity for CAM photosynthesis and vegetative propagation via leaf epiphylls is well established, and both attributes are clearly manifested in B. pinnatum [1].

B. Geographic Distribution and Traditional Cultivation

Although endemic to Madagascar, B. pinnatum has achieved a pantropical distribution through anthropogenic dispersal and naturalization in warm, humid regions worldwide. This species is frequently categorized as invasive owing to its prolific colonization of moist, shaded habitats spanning low altitudes to elevations of approximately 8,500 feet [12]. In Brazil, its occurrence has been documented across all five geopolitical macroregions — Northeast, North, Southeast, Midwest, and South — with particular abundance in littoral zones and the Caatinga biome [14]. The plant is equally well documented in the Indian subcontinent, notably in West Bengal, Odisha, and the Western Ghats, and has been recorded in Nigeria, Ghana, Cameroon, Trinidad and Tobago, China, Indonesia, the Philippines, and Indochina [1], [12], [15]. Regarding domestic consumption in India, the National Medicinal Plants Board and the Indian Council of Forestry Research and Education projected an annual utilization of approximately 0.00075 million metric tons, with a corresponding commercial trade volume of 90 MT [5].

This species is widely cultivated in domestic gardens and colonizes anthropogenically disturbed habitats, attributable to its considerable tolerance to shade, nutrient-deficient substrates, and minimal horticultural intervention. Propagation is readily achieved through detached leaf epiphylls or stem segments [12], [13]. B. pinnatum is recognized by a diverse array of vernacular names across linguistic traditions. In Hindi, it is denoted as "Patharchatta" or "Jakh Me Hayat"; in Sanskrit as "Parnabija" or "Pashanabheda"; in Bengali as "Koppata" or "Patharkuch"; in Telugu as "Simahmudu"; in Tamil as "Ranakalli"; in Malayalam as "Ellamurunga"; and in Hawaiian as "Oliwa-ku-kahakai" or "Lao di sheng gen." Across Yoruba-speaking regions of Africa, the designation "Hoja del aire" is in common usage, while in Brazil the plant is colloquially termed "saião," "coirama," "fortuna," or "roda-da-fortuna." In Anglophone territories, the prevalent common names include "life plant," "love plant," "wonder leaf," "air plant," "cathedral bells," "Canterbury bells," and "Goethe plant" [1], [15].

C. Plant Parts Used in Medicine

Among the various plant organs of B. pinnatum, the leaf is the most extensively investigated and therapeutically exploited part across diverse ethnomedicinal systems, owing to its year-round availability, ease of harvest, and high concentration of bioactive constituents [5], [16]. Preparations derived from the whole plant, including the stem, root, and floral structures, continue to serve specific traditional therapeutic purposes [1], [5]. Both leaf and stem tissues are administered in diverse pharmacognostical forms, including freshly expressed juice, aqueous decoctions, hydroethanolic extracts (50% v/v ethanol), absolute ethanol extracts, methanolic extracts, and topical poultices for dermatological disorders, owing to their pronounced bitter taste and potent astringent character, which confers efficacy against gastrointestinal disturbances such as diarrhea, flatulence, and emesis [5], [14]. Fresh foliage and expressed juice are administered orally or applied topically to manage hepatic dysfunction, peptic ulceration,

diabetes mellitus, arterial hypertension, respiratory ailments, cutaneous wounds, thermal burns, and abscess formation. Within the frameworks of Ayurveda and Indian homeopathic medicine, freshly expressed leaf juice, desiccated leaf powder, and aqueous decoctions are employed in the treatment of smallpox, otitis, bronchial asthma, nephrolithiasis (colloquially designated as "stone-dissolver" or "Pashanabheda"), and rheumatic disorders. The World Health Organization formally acknowledges B. pinnatum as an ethnomedicinal plant of significance for primary healthcare provision in resource-limited settings, where access to conventional pharmaceuticals remains restricted [16], [17].

III. PHYTOCHEMICAL CONSTITUENTS

A. Bufadienolides

Bufadienolides are a structurally distinctive class of C-24 steroidal compounds bearing multiple hydroxyl substituents. The defining structural characteristic of this compound class is the occurrence of a six-membered α-pyron (2H-pyran-2-one) lactone ring at the C-17β position, a moiety fundamentally responsible for their pronounced cardioactive properties, principally through potent inhibition of the sarcolemmal Na+/K+-ATPase pump [5]. The principal bufadienolide constituents isolated from Bryophyllum species include bersaldegenin-1-acetate, bersaldegenin-3-acetate, bersaldegenin-1,3,5-orthoacetate, and bryophyllin A (synonymous with bryotoxin C). Phytochemical characterization of B. pinnatum has yielded eight structurally distinct bufadienolides in leaf, floral, stem, and root tissues [8]. In addition, bryophyllin B, bryophyllin C, bryotoxin A, bryotoxin B, and the 1,3,5-orthoacetate derivatives daigremontianin and daigremontianin-1-acetate have been documented. The recurring 1,3,5-orthoacetate motif serves as a chemotaxonomic distinguishing feature within this genus [1], [8]. Notably, bersaldegenin-1,3,5-orthoacetate and bryophyllin A exhibited substantial cytotoxic efficacy in vitro against neoplastic cell lines of oral cavity, pulmonary, and intestinal origin. The bufadienolide fraction has also been implicated in the attenuation of Epstein-Barr virus replication [5].

The quantitative determination of bufadienolides in B. pinnatum leaf tissue and cold-pressed juice was accomplished via ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS), revealing concentrations spanning 3.78–40.50 mg per 100 g of lyophilized plant material, with juvenile leaf tissue exhibiting comparatively elevated concentrations. The standard isolation protocol entails the initial maceration of desiccated plant material in methanol or ethanol, sequential liquid-liquid partitioning with ethyl acetate and n-hexane, and subsequent chromatographic purification employing Sephadex LH-20 size-exclusion gel filtration, silica-gel open-column chromatography, and semi-preparative HPLC as the terminal fractionation step [1], [5]. The considerable inter-organ and inter-seasonal variability in bufadienolide accumulation poses a substantial impediment to the development of reproducible and standardized phytopharmaceutical preparations from B. pinnatum [14], [18].

B. Flavonoid Glycosides

B. pinnatum harbors a structurally diverse repertoire of O-glycosylated flavonoids, predominantly attributable to two subclasses: flavonols, including quercetin, kaempferol, isorhamnetin, and myricetin, and flavones, encompassing luteolin, acacetin, diosmetin, and apigenin. Leaf tissue contains flavanones, most notably naringenin, in addition to aurones, anthocyanidins, isoflavonoids, and chalcones [5], [18]. Two predominant flavonoid constituents, quercetin-3-O-α-L-arabinopyranosyl (1→2) and its structurally related minor congeners, are recurrently detected and widely regarded as diagnostic phytochemical markers for species authentication. Additional glycosidic constituents of phytochemical significance include rutin, isoquercitrin, miquelianin, astragalin, luteolin-7-glucoside, hyperoside, isorhamnetin-3-O-rutinoside, naringenin, diosmin, and acacetin-7-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, each of which exhibits structurally unique glycosylation patterns [1], [5], [19].

Quantitative profiling of the principal glycosidic constituents Bp1, Bp2, and Bp3 in a standardized hydroethanolic leaf extract was accomplished via a validated ultra-fast liquid chromatography-diode array detection (UFLC-DAD) protocol, yielding concentrations of 35.56 ± 0.086 mg, 4.66 ± 0.076 mg, and 4.56 ± 0.026 mg per gram of dry extract, respectively, with coefficients of determination exceeding $r > 0.9988$ across the linear range [9], [20]. Quercetin-derived flavonoids exhibit pronounced radical-scavenging capacity, suppress pro-inflammatory cytokine biosynthesis, and modulate membrane transporter and metabolic enzyme activity via stereospecific molecular interactions [5], [18]. High-performance liquid chromatography with diode array detection (HPLC-DAD) interfaced with electrospray ionization mass spectrometry, in conjunction with LC-MS/MS dereplication strategies, is the analytical platform of choice for the comprehensive characterization of O-glycosylated flavonoid derivatives [18], [20].

C. Triterpenes

Pentacyclic triterpenoids of the oleanane, ursane, lupane, and friedelane skeletal types, along with sterols and phytosterols that preferentially accumulate in bark tissues and epidermal leaf waxes, represent an additional phytochemical class of considerable pharmacological relevance [5], [8], [21]. Among these, friedelin has the most intricate biosynthetic origin, requiring

a cascade of oxidative skeletal rearrangements via cationic intermediates. Functional characterization of the cognate oxidosqualene cyclase genes responsible for friedelin biosynthesis, first elucidated in Kalanchoe daigremontiana, demonstrated the exclusive epidermal localization of these enzymes, which also govern the biosynthesis of lupeol, taraxerol, and glutinol. Friedelin, glutinol, glutanol, glutinol acetate, epifriedelanol, germanicol, and an α-/β-amyrin mixture have been identified as the major triterpenoid constituents of the leaf epicuticular wax of B. pinnatum [1]. The broader triterpenoid inventory encompasses bryophynol, bryophollone, bryophollenone, α- and β-amyrin and their respective acetate esters, α- and β-amyrin-β-D-glucopyranoside, β-sitosterol, and a range of additional constituents, including taraxasterol, pseudo-taraxasterol, taraxerol, taxaxerone, 18α-oleanane, glut-5-en-3β-ol, glut-5-en-3-one, and ursolic acid. The co-occurrence of bryophynol and bryophollone augments the chemotaxonomic characterization of B. pinnatum in Crassulaceae. β-Sitosterol, in combination with bryophyllin A, has attracted particular interest because of its demonstrated docking affinity for VEGFR2, PI3K, and c-Met in hepatocellular carcinoma models. Isolation was achieved by sequential extraction with n-hexane and dichloromethane, followed by silica gel column chromatography and terminal purification via recrystallization or preparative thin-layer chromatography (TLC), with structural elucidation accomplished using mass spectrometry and mono- and bidimensional nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy [1], [5].

D. Phenolic Acids and Other Constituents

The phenolic acid fraction of B. pinnatum is represented by two principal structural series: benzoic acid derivatives, including p-hydroxybenzoic, protocatechuic, vanillic, gallic, and syringic acids, and cinnamic acid derivatives, comprising p-coumaric, caffeic, chlorogenic, ferulic, and 4-hydroxy-3-methoxycinnamic acids. The aliphatic organic acid profile of the aerial parts encompasses citric, isocitric, oxaloacetic, oxalic, malic, and succinic acids, with phosphoenolpyruvate detected in vegetative tissues [5], [19]. Carbohydrate profiling has established the occurrence of glucose, fructose, galactose, lactose, raffinose, and sucrose, as well as condensed tannins, the wax alkanes hentriacontane and n-triacontane, and a series of long-chain n-alkane homologues spanning chain lengths of C25–C35 and C26–C34 [5].

Reports of minor alkaloid constituents exist but are inconsistent across independent investigations, suggesting that alkaloid accumulation in B. pinnatum is regulated by genotypic variation, ontogenetic stage, or prevailing environmental stimuli. Other constituents include polysaccharidic macromolecules, trace-level volatile terpenoids associated with the essential oil fraction, and phenanthrene-type polyaromatics such as 2-(9-decenyl)-phenanthrene, 2-(9-undecenyl)-phenanthrene, and 1-ethanamino-7-yne-5'-oxophenanthrene. Quantitative assessments have consistently demonstrated that the secondary metabolite composition of B. pinnatum is subject to substantial plasticity as a function of geographical provenance, agroclimatic conditions, phenological stage of collection, organ specificity, leaf ontogeny and extraction methodology. For example, antileishmanial flavonoid concentrations are markedly higher in summer-harvested leaves subjected to aqueous extraction at 50°C [1], [14], [18]. This inherent phytochemical heterogeneity, compounded by the absence of harmonized extraction protocols across research settings, constitutes a formidable barrier to the development of B. pinnatum as a standardized phytomedicine. As underscored by recent critical appraisals[4], [22], [23], the establishment of validated quantitative chemical markers, notably the Bp1/Bp2/Bp3 flavonoid triad and bersaldegenin-1,3,5-orthoacetate, alongside the adoption of good manufacturing practices, represents an indispensable prerequisite for future phytopharmaceutical development.

Compound Name	Chemical Class	Plant Part(s) Detected	Reported Concentration	Detection / Quantification Method	In-text Citation
Bersaldegenin-1-acetate	Bufadienolide	Leaf; whole plant; aerial parts	Total of 4 bufadienolides: 3.78–40.50 mg/100 g dry weight (leaves)	UHPLC-MS/MS	[1]
Bersaldegenin-1,3,5-orthoacetate	Bufadienolide	Leaf; floral (flowers in B. delagoense)	Total of 4 bufadienolides: 3.78–40.50 mg/100	UHPLC-MS/MS	[1]

			g dry weight (leaves)		
Bersaldegenin-3-acetate	Bufadienolide	Leaf; whole plant; aerial parts	Total of 4 bufadienolides: 3.78–40.50 mg/100 g dry weight (leaves)	UHPLC-MS/MS	[1]
Bryophyllin A (= bryotoxin C)	Bufadienolide	Leaf; floral (flowers, leaves/stems); root	Total of 4 bufadienolides: 3.78–40.50 mg/100 g dry weight (leaves)	UHPLC-MS/MS	[1]
Bryophyllin B	Bufadienolide	Leaf; whole plant	—	—	[1]
Bryophyllin C	Bufadienolide	Leaf	—	—	[1], [12]
Bryotoxin A	Bufadienolide (glycoside)	Floral; stem; root	—	—	[1]
Bryotoxin B	Bufadienolide (glycoside)	Floral; stem; root	—	—	[1]
Daigredorigenin-3-acetate	Bufadienolide	Aerial parts	—	—	[1]
Daigremontianin	Bufadienolide	Aerial parts	—	—	[1]
Kalantuboside A	Bufadienolide (glycoside)	Whole plant	—	—	[1]
Kalantuboside B	Bufadienolide (glycoside)	Whole plant	—	—	[1]
Methyl daigremonate	Other (opened-lactone congener)	Leaf	—	—	[1]
3,5,7,3′,5′-Pentahydroxyflavone	Flavonoid Glycoside	Whole plant	—	—	[1]
3′,4′-Di-O-methylquercetin	Flavonoid Glycoside	Leaf	—	—	[1]
Acacetin 7-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	Flavonoid Glycoside	Leaf	—	—	[1]
Afzelin (kaempferol 3-O-α-L-rhamnopyranoside)	Flavonoid Glycoside	Whole plant	—	—	[1]
α-Rhamnoisorobin (kaempferol 7-O-α-L-rhamnopyranoside)	Flavonoid Glycoside	Whole plant	—	—	[1]
Apigenin	Flavonoid Glycoside	Leaf	—	—	[12]
Astragalin (kaempferol-3-O-β-D-glucopyranoside)	Flavonoid Glycoside	Leaf	—	—	[1], [12]

Catechin	Flavonoid Glycoside (flavanol)	Leaf	—	—	[18]
Diosmine (diosmetin 7-O-rutinoside)	Flavonoid Glycoside	Leaf	—	—	[1]
Epicatechin	Flavonoid Glycoside (flavanol)	Leaf	—	—	[18]
Epigallocatechin	Flavonoid Glycoside (flavanol)	Leaf	—	—	[18]
Epigallocatechin-3-O-syringate	Flavonoid Glycoside	—	—	—	[1]
Isoquercitrin (quercetin 3-O-β-D-glucopyranoside)	Flavonoid Glycoside	Floral	—	—	[1]
Kaempferitrin (kaempferol 3-O,7-O-di-α-L-rhamnopyranoside)	Flavonoid Glycoside	Whole plant	—	—	[1]
Kaempferol	Flavonoid Glycoside	Leaf	—	—	[1], [12]
Kaempferol 3-O-α-D-glucopyranoside 7-O-α-L-rhamnopyranoside	Flavonoid Glycoside	Whole plant	—	—	[1]
Kaempferol 3-O-α-L-(2-O-acetyl)rhamnopyranoside 7-O-α-L-rhamnopyranoside	Flavonoid Glycoside	Whole plant	—	—	[1]
Kaempferol 3-O-α-L-(3-O-acetyl)rhamnopyranoside 7-O-α-L-rhamnopyranoside	Flavonoid Glycoside	Whole plant	—	—	[1]
Kaempferol 3-O-α-L-(4-O-acetyl)rhamnopyranoside 7-O-α-L-rhamnopyranoside	Flavonoid Glycoside	Whole plant	—	—	[1]
Kaempferol 3-O-β-D-xylopyranosyl-(1→2)-α-L-rhamnopyranoside	Flavonoid Glycoside	Leaf	—	—	[1]
Kapinnatoside (kaempferol 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside)	Flavonoid Glycoside	Leaf	—	—	[1], [12]
Luteolin	Flavonoid Glycoside	Leaf	—	—	[1], [12]
Luteolin 7-O-β-D-glucopyranoside	Flavonoid Glycoside	Leaf	—	—	[1]
Miquelianin (quercetin 3-O-β-D-glucuronopyranoside)	Flavonoid Glycoside	Floral (flowers)	—	—	[1]

Myricetin 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside	Flavonoid Glycoside	Leaf	—	—	[1]
Myricitrin (myricetin-3-O-α-L-rhamnopyranoside)	Flavonoid Glycoside	Leaf	—	—	[1]
Quercetin	Flavonoid Glycoside	Leaf	—	—	[1], [12]
Quercetin 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside	Flavonoid Glycoside	Leaf; floral	—	—	[1]
Quercetin 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside 7-O-β-D-glucopyranoside	Flavonoid Glycoside	Leaf	—	—	[1]
Quercetin 3-O-diarabinoside	Flavonoid Glycoside	Leaf	—	—	[1], [12]
Quercitrin (quercetin 3-O-α-L-rhamnopyranoside)	Flavonoid Glycoside	Leaf; floral	—	—	[1], [12]
Rutin (quercetin 3-O-rutinoside)	Flavonoid Glycoside	Leaf	—	—	[1], [12]
18α-Oleanane	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8]
3β-Friedelanol (epifriedelanol)	Triterpene-Sterol	Leaf (leaf wax)	—	Mass spectrometry	[1], [8]
α-Amyrin	Triterpene-Sterol	Aerial parts / leaf	—	—	[1], [12]
α-Amyrin-β-D-glucopyranoside	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8]
β-Amyrin	Triterpene-Sterol	Aerial parts	—	—	[1], [12]
β-Sitosterol	Triterpene-Sterol	Leaf / aerial parts	—	—	[12]
β-Sitosterol-3-O-glucoside	Triterpene-Sterol	— (reported in B. delagoense)	—	—	[1]
Bryophyllol	Triterpene-Sterol	Leaf	—	—	[12]
Bryophollenone	Triterpene-Sterol	—	—	—	[1], [8], [12]
Bryophollone	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8], [12]
Bryophynol	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8], [12]
Glut-5-en-3-one	Triterpene-Sterol	Leaf	—	—	[1], [8]

Glutinol	Triterpene-Sterol	Leaf wax / aerial parts	—	Mass spectrometry	[1], [12]
Pseudo-taraxasterol	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8], [12]
Stigmasterol	Triterpene-Sterol	Shoot / dried leaves	—	—	[1], [12]
Taraxerone	Triterpene-Sterol	Leaf / aerial parts	—	—	[1], [8]
Taraxerol	Triterpene-Sterol	Aerial parts	—	—	[12]
4-Hydroxy-3-methoxy-cinnamic acid	Phenolic Acid-Organic Acid	—	—	—	[1]
4′-O-β-D-glucopyranosyl-cis-p-coumaric acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Caffeic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
Cinnamic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
Citric acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Ferulic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
Gallic acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Isocitric acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Malic acid	Phenolic Acid-Organic Acid	Whole plant	Large amounts (no quantitative figure stated)	—	[1]
Oxalic acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Oxaloacetate	Phenolic Acid-Organic Acid	—	—	—	[1]
p-Coumaric acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
p-Hydroxybenzoic acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Phosphoenolpyruvate	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
Protocatechuic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]

Succinic acid	Phenolic Acid-Organic Acid	—	—	—	[1]
Syringic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[1], [12]
Syringic acid β-D-glucopyranosyl ester	Phenolic Acid-Organic Acid	—	—	—	[1]
Vanillic acid	Phenolic Acid-Organic Acid	Aerial parts	—	—	[12]

TABLE 1: SUMMARIZES THE MAJOR BUFADIENOLIDES, FLAVONOID GLYCOSIDES, TRITERPENES, AND PHENOLIC ACIDS IDENTIFIED IN *B. PINNATUM*, ALONG WITH THEIR PLANT-PART LOCALIZATION AND REPORTED CONCENTRATIONS.

IV. PHARMACOLOGICAL ACTIVITIES

A. Anti-inflammatory Activity

The most solid piece of evidence for the inflammatory effects of B. pinnatum is its activity in rodent models of colitis. In the paper [20] in the journal Frontiers in Pharmacology, it was shown that oral application of 100 and 200 mg/kg of hydroethanol leaf extract of B. pinnatum to mice reduced the length of intestines and alleviated inflammation and ulceration in the model of dinitrobenzene sulfur and dextran sulfate sodium colitis [20]. The mechanism includes inhibition of TLR-4, NF-κB65, IL-17, COX-2, MCP-1, MIP-2, ICAM-1, TNF, IL-1, IL-6, and iNOS expression in colones of DSS-challenged mice [20].

Regarding chronic gastric ulcers, B. pinnatum leaf extract (250 and 500 mg/kg) has shown to reduce the ulcer index, increase the concentration of glutathione, decrease the myeloperoxidase enzyme activity, inhibit the secretion of IL-1 and TNF-alpha, elevate IL-10 and the expressions of COX-2 and NF-kappa Bp65 [9]. Concerning the phytochemistry profile, the major components were found to be quercetin 3-O-L-arabinopyranosyl-(1→2)-O-L-rhamnopyranoside (Bp1; 33.12 mg/g) and the co-principal fractions of kaempferol and quercetin glycoside [9]. Additionally, a complementary study conducted by Ferreira et al. showed the effects of the major flavonoid fraction of B. pinnatum with the ability to reduce the migration of leukocytes in ID50= 2.0 mg/kg i.v. carrageenan-induced depression, reducing craniol ear edema and inhibiting both COX-1 and COX-2 with associated reduction of TNF [24].

Limitations*:* All findings derive from rodent or in vitro models; no clinical anti-inflammatory trial with *B. pinnatum* has been reported.

B. Anticancer Activity

The B. pinnatum (syn. Kalanchoe pinnata) causes selective cytotoxicity on cancer cell lines via ROS-induced apoptosis. Faundes-Gandolfo et al. observed that the leaf ethanol extract had antiproliferative effects on HT-29 (colon), MCF-7 (breast), PC-3 (prostate), and non-cancerous CCD 841 CoN cells, with IC50 ranging from 0.20 to 14.45 g/mL [25]. Importantly, the extract showed higher specificity to the HT-29 colon cancer cells (SI = 8.40) than CoN cells (MCF-7 SI = 0.66; PC-3 SI = 0.11) due to ROS generation and caspase activation leading to cell apoptosis [25]. Mechanistically, the potential of the mitochondrial membrane was altered and there was increased condensation and fragmentation of chromatin, which are features of intracellular apoptosis [25].

For example, in cervical cancer, the chloroform extract of the leaves of B. pinnata caused cytotoxicity in HeLa cells, and bufadienolide bersaldegenin-1,3,5-orthoacetate was detected as an active compound resulting from G2/M phase-specific cell cycle inhibition and caspase-independent cell death in HeLa cells [5], [26]. In the in vitro studies on HeLa and SiH cervicals, quercetin (the primary flavonoid of K. pinnata) regulates ERK1/2 phosphorylation, apoptosis, and migration [27]. Apoptosis has been confirmed in the studies by means of caspase-3/9 activation, Bcl-2/Bax ratio change, PARP cleavage, and cell cycle arrest in phases G2/M or S [1], [25], [27]. Limitation: The available data are primarily in vitro; there is still a need for in vivo tumor xenograft or allograft studies.

C. Antidiabetic Activity

The carbohydrate-digesting enzymes α-amylase (IC_{50} = 126.15 ± 9.76 µg/mL) and α-glucosidase (IC_{50} = 149.20 ± 14.44 µg/mL) were inhibited by B. pinnatum aqueous extract, according to Ojo et al. (Ojo et al., 2018). The ethyl acetate fraction exhibited the

strongest inhibition (α-amylase IC_{50} = 62.45 µg/mL; α-glucosidase IC_{50} = 70.90 µg/mL). This implies the possibility of postprandial glycemic control that is conceptually similar to acarbose.

The in vivo testing was performed in normal and streptozotocin-induced diabetic Wistar rats where significant (P< 0.05-0.001) hypoglycemic activities were exhibited using an aqueous extract from leaves of B. pinnatum at 25-800 mg/kg p.o. The possible modes of action involved zinc content and immunomodulatory flavonoids[1], [5]. Aransiola et al. and Menon et al. [14] found that aqueous leaf extracts caused reduction in blood glucose levels, increase in catalase and Mg-ATPase activity in STZ-diabetic Sprague-Dawley rats. Further, a 21 days administration of ethanolic extract caused hypolipidemic activity in Wistar rats by lowering total cholesterol and increasing HDL [14]. It is known that topical ethanolic extract demonstrates wound healing properties (diabetic ulcers) on Sprague-Dawley rats (86.3% wound healing by day 11 vs 68.0% wound healing in controls) [1], [28].

Limitations: No randomized clinical trials; the diabetes-relevant aldose reductase inhibition remains to be characterized in *B. pinnatum* extracts.

D. Antiviral Activity

It has been proven that Bx. pinnatum possesses antiviral properties against a variety of viruses. Human alpha-herpes viruses 1 and 2 and the vaccinia virus were inhibited by compounds KPB-100 and KPB-200 from K. pinnata root extracts; compound KPB-100 inhibited all viruses under study [29]. The antibacterial activity of bryophyllin A against Epstein-Barr virus has also been proved; Bersaldegenin and daigremontianin showed activity against EBV [29]. Moreover, derivatives of kaempferol from Bryophyllum daigremontianum proved to be active against HSV-1 and HSV-2, and bryophyllin B was recognized as an efficient inhibitor of HIV infection [13], [18].

In silico molecular docking identified 21 B. pinnatum constituents with binding energies below -8.9 kcal/mol against viral sites, relevant to SARS-CoV-2 [7]. Bryotoxin B had the strongest binding to the spike protein (−9.9 kcal/mol), followed by β-amyrin acetate (−9.5 kcal/mol) and diosmin (−9.4 kcal/mol). Diosmin also had the highest affinity for ACE2 (−9.0 kcal/mol) [7] Souza et al. found that quercetin, rutin, astragalin, and luteolin had spike affinities of < −9.0 kcal/mol. Aurora et al. (cited in [5]) discovered that rutin, along with astragalin, luteolin, quercetin, kaempferol, taxifolin, and narcissin, inhibits the SARS-CoV-2 main protease; rutin also demonstrated stable contact with the spike protein and ACE2 in molecular dynamics simulations [5]. Key point to consider: These are all just dockings; experimental confirmation is not yet available, and further in vitro and in vivo studies will need to be carried out before making any therapeutic claim [5], [7].

Activity Category	Extract Type and Dose	Experimental Model	Key Molecular Targets / Markers Affected	Quantitative Outcome	Citation
Anti-inflammatory	Aqueous leaf extract, 400 mg/kg b.w., p.o.	Wistar rats — paw edema assay	Pro-inflammatory paw edema volume	Significant reduction of acute inflammation (87.3% reduction vs. control); p.o. dose-dependent	[1]
Anti-inflammatory	Steroidal compound stigmast-4,20,23-trien-3-one, 300 mg/kg b.w., p.o.	Wistar rats — paw edema assay	Pro-inflammatory paw edema volume	84.5% reduction; identified as main anti-inflammatory constituent in ethanolic extract	[1]
Anti-inflammatory	Ethanolic leaf extract, 0.1–0.5 mg/ear	Swiss albino mice — croton oil / capsaicin / phenol-induced ear edema	Irritant-agent-induced ear swelling	Significant inhibition of ear edema with 0.1 or 0.5 mg/ear (depending on	[1]

				irritant); dose-selective	
Anti-inflammatory	Aqueous flower extract + quercetin diglycoside	Swiss mice — croton oil ear edema and carrageenan-induced pleurisy	TNF-α in pleural exudate; leucocyte migration	Significant reduction of TNF-α levels and leucocyte migration mediated by extract and by compound 29	[1]
Anti-inflammatory	Aqueous leaf extract	Healthy volunteers (anthroposophic pharmaceutical use)	Ex vivo LPS-stimulated whole-blood TNF-α release	No pharmacologically relevant influence on cytokine release at the doses used	[1]
Anti-inflammatory	Leaf press juice / pressed juice (anthroposophic preparation)	Guinea pigs — histamine-induced gastric ulceration	Histamine-induced ulcerogenesis	Pretreatment did NOT prevent the development of histamine-induced ulcerations in guinea pigs	[1]
Anti-inflammatory (anti-ulcer; ulcer healing)	Methanolic fraction of B. pinnatum, 100 or 300 mg/kg b.w., i.p.	Rats — acute gastric ulcer models + acetic acid-induced ulcer	Gastric lesion formation / ulcer healing	Significant inhibition of acute gastric ulcer development at both doses; improved healing of acetic acid-induced gastric ulcers	[1]
Anti-inflammatory (anti-ulcer)	Ethanolic leaf extract, 10–40 mg/kg b.w.	Rats — indomethacin-induced gastric ulcer	Indomethacin-induced ulcer lesions	Inhibition of indomethacin-induced gastric ulceration across the 10–40 mg/kg dose range	[1]
Anticancer (antitumor promoting)	Five bufadienolides isolated from B. pinnatum + B. daigremontianum × tubiflorum	Epstein–Barr virus early antigen activation assay in vitro	EBV-EA activation (chemopreventive marker)	All five compounds inhibited EBV-EA activation; 1,3,5-orthoacetate moiety critical for activity	[1]
Anticancer	Pure bryophyllin A, applied as isolated bufadienolide	A-549 (lung carcinoma); KB (keratin-forming tumor); HCT-8 (colon carcinoma) cells	Cytotoxicity	ED50 = 10 ng/mL; ED50 = 14 ng/mL; ED50 = 30 ng/mL	[1]

Anticancer	Pure bersaldegenin -3-acetate	HCT-8 (colon carcinoma) cells	Cytotoxicity	ED50 = 10 ng/mL	[1]
Anticancer	Pure bryophyllin B (isolated bufadienolide)	KB (keratin-forming tumor) cells	Cytotoxicity	ED50 < 80 ng/mL	[1]
Anticancer	Pure kalantuboside B and bersaldegenin -1,3,5-orthoacetate (isolated from B. delagoense)	A2058 (melanoma) and HL-60 (leukemia) cell lines	Cytotoxicity	IC50 = 0.01 µM for both compounds against A2058 and HL-60	[1]
Anticancer	Bersaldegenin -1,3,5-orthoacetate and daigremontianin (isolated)	Induced Raji cell line	Cytotoxicity / EBV inhibition	Cytotoxic effect against Burkitt's lymphoma; inhibition of Epstein–Barr virus	[18]
Anticancer	Methanol leaf + stem extract, 400–1600 µg/mL	HeLa cervical cancer cells; A549 lung adenocarcinoma; T47D, MDA-MB-231 breast lines; PC-3 prostate; HepG2 liver	Cytotoxicity	Significant growth inhibition in all six cell lines from 400 µg/mL upwards; methanol and flavonoid fractions the most cytotoxic	[1]
Anticancer	Aqueous B. pinnatum leaf extract	NIH/3T3 mouse fibroblasts (non-tumor control)	Basal viability	Non-cytotoxic to NIH/3T3 cells (selective window)	[1]
Anticancer	B. delagoense water-soluble ethanolic fraction, 10 and 100 mg/kg b.w. 5×/wk × 6 wk	Nude mice — A549 lung cancer xenograft in vivo	Tumor growth	Significant reduction of tumor growth at 10 and 100 mg/kg; cell-cycle arrest and senescence induction in vitro	[1]
Anticancer	Aqueous B. pinnatum leaf extract	Ehrlich ascites tumor in vivo	Tumor volume, tumor weight; survival; kidney/liver weights	Significant, dose-dependent decrease in tumor volume and tumor weight vs. control; dose-dependent modulation of body and organ weights; favorable	[1]

				histopathology with more apoptotic cells	
Anticancer	Aqueous B. pinnatum leaf extract	In vivo antigenotoxicity study (cyclophosphamide-induced)	Chromosomal aberrations and micronuclei	Significant, dose-dependent reduction of cyclophosphamide-induced chromosomal aberrations and micronuclei	[1]
Anticancer	Aqueous B. pinnatum leaf extract, 350 mg/kg/day p.o.	BALB/c mouse CT26 colon carcinoma	Tumor volume; NK cell function	No effect on tumor volume or proliferation; slightly impaired NK cell function	[1]
Anticancer	Pure bryophyllin B	KB (oral keratin-forming), A-549 (lung), HCT-8 (colon) cell lines	Cytotoxicity	Confirmed potent cytotoxicity in this compilation review;	[18]
Anticancer	Bersaldegenin derivatives (B. pinnatum / daigremontianum × tubiflorum)	MCF-7 breast; NCI-H460 lung; SF-268 glioblastoma	Cytotoxicity	MCF-7, NCI-H460, SF-268 cells affected by bryophyllin A and B + bersaldegenins	[18]
Antidiabetic	Aqueous leaf extract, 25–800 mg/kg b.w., p.o.	Normoglycemic and streptozotocin-induced diabetic Wistar rats in vivo	Plasma glucose; glucose tolerance	Significant ($P < 0.05$–0.001) hypoglycaemia; significant reduction in blood glucose over a 30–120 min window in STZ-induced diabetic rats; also analyzed serum lipid profile and tail-vein blood glucose kinetics	[1], [12]
Antidiabetic	Ethanolic extract (and combined with T. africana leaf ethanol extract, equal mixture)	Albino rats, oral administration for 21 days	Plasma glucose; glycaemic status; lipid profile	Significant reduction in STZ-induced diabetic rats ($P < 0.05$) across varying mixture ratios; modulation of lipid-protein markers and zinc content reported as contributing hypoglycaemic factor	[12]

Antiviral	Kaempferol derivatives isolated from B. daigremontianum	In vitro assay — HSV-1 and HSV-2	Herpes Simplex Virus (HSV-1 / HSV-2) replication	Reported antiviral activity of kaempferol derivatives against HSV-1 and HSV-2 (specific IC50 not stated in available excerpt)	[18]
Antiviral	Pure bryophyllin B from B. pinnatum	In vitro assay — Human Immunodeficiency Virus	HIV replication	Reported as a potent HIV inhibitor (specific IC50 / selectivity index not stated in available excerpt)	[18]
Antiviral	Ethanolic leaf extract (aqueous / methanol fractions)	In vitro anti-papillomavirus assay via culture system assessing HPV	Human papillomavirus	Higher activity of the extract than the steroidal fraction against HPV (the fraction more potent than the extract against cervical cancer cells); HPV pivotal in cervical cancer development	[1]
Antiviral	Aqueous leaf extract (oral / i.v. / i.p. / topical)	BALB/c mice — Leishmania promastigote/amastigote model (relevant to parasite-driven viral co-factors)	IgG antibody titer (parasite-specific)	Reduction of IgG titers to 20% vs. untreated mice after oral, i.p., or topical application	[1]

TABLE 2: SUMMARIZES THE REPORTED ANTI-INFLAMMATORY, ANTICANCER, ANTIDIABETIC, AND ANTIVIRAL ACTIVITIES OF *B. PINNATUM* EXTRACTS, INCLUDING EXPERIMENTAL MODELS AND KEY QUANTITATIVE OUTCOMES.

V. MOLECULAR MECHANISMS AND SIGNALING PATHWAYS

A. PI3K/AKT Pathway

The PI3K/AKT/mTOR pathway regulates cell survival, proliferation, and anti-apoptotic activities in cancer. PI3K catalyzes the phosphorylation of 3′-OH group of phosphatidylinositol to form PIP3 that recruits AKT to the plasma membrane through PH domain. Activation of AKT phosphorylates various targets such as GSK3β, FOXO, BAD, and MDM2, which promotes cell proliferation and angiogenesis. mTORC1 functions as a master regulator of cell growth[27].

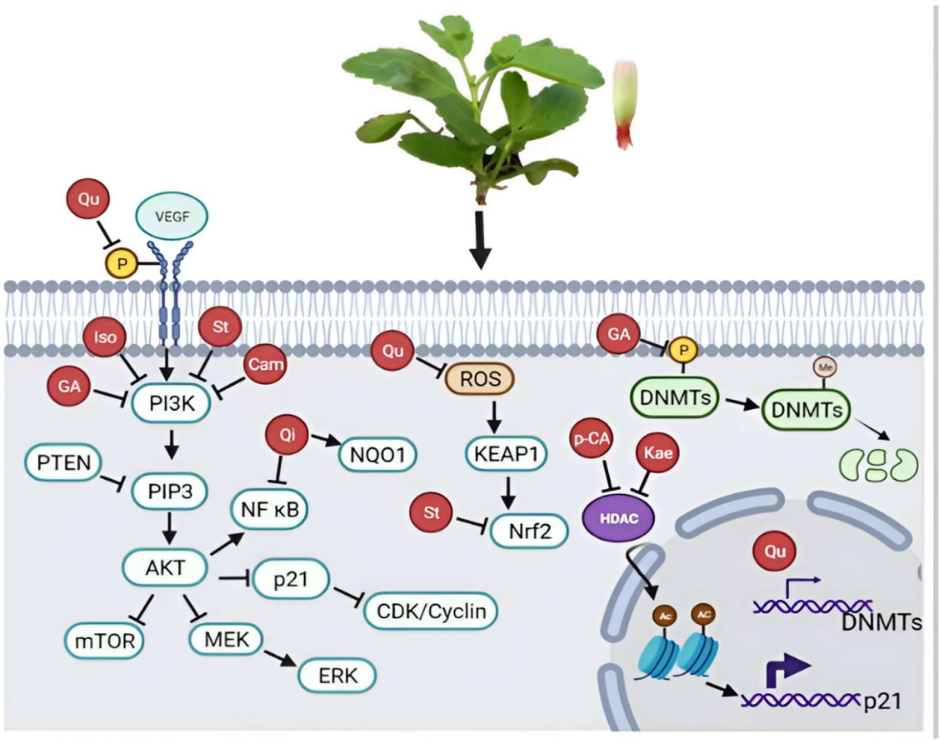

Fig. 1. Dual role of Nrf2 in modulating HO-1-mediated antioxidant defense and NF-κB-driven pro-inflammatory signaling: inhibitory crosstalk between the two pathways.[30]

The phytochemicals of B. pinnatum seem to exert effects on this pathway through a number of converging mechanisms. For instance, gallic acid has been found in lung, ovarian, and glioma cancer cells to lower the level of proteins like PI3K, p-AKT, and mTOR. As such, they affect viability, proliferation, invasion, and angiogenesis. Caffeic acid showed great ability to decrease the p-AKT in colorectal cancer stem cells, while quercetin binds with PI3K in prostate, breast, and pancreatic cells, which causes decreased AKT phosphorylation leading to apoptosis via Bax/Bcl-2 and p53 regulation [5], [27].

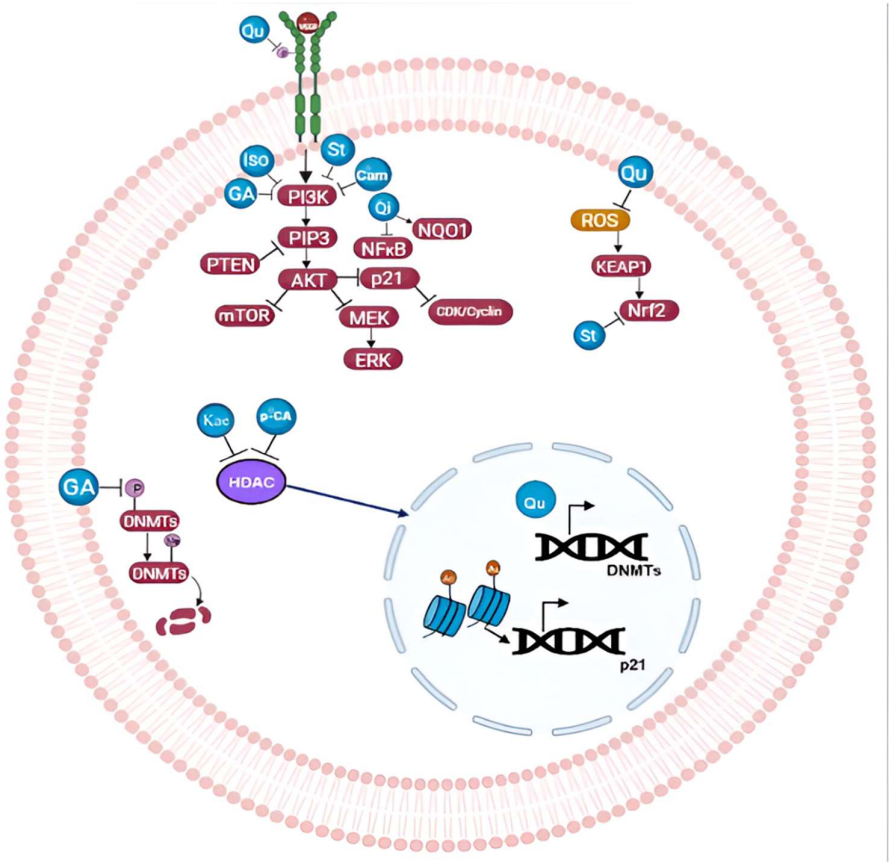

Fig. 2. Therapeutic inhibitors targeting key nodes of the canonical Wnt/β-catenin signaling pathway, from ligand-receptor interaction to nuclear transcription of target genes.[31]

Similar to this process, it was discovered that kaempferol combined with erlotinib is able to inhibit PI3K/AKT in PANC-1 and BxPC-3 pancreatic cancer cells, which confirms the importance of PI3K/AKT as an oncology target [27]. The B. pinnatum species could be considered as a prospective adjuvant capable of producing anticancer effects through the modulation of PI3K/AKT survival pathway. However, this information comes from in vitro experiments only.

B. NF-κB and TLR4 Pathway

NF-κB regulates inflammation perfectly. There are two major pathways, where one of them consists of the phosphorylation and destruction of IκB-α via the IKK complex, thus allowing NF-κB p65 to enter the nucleus and bind to the κ-B site. This leads to the expression of TNF-α, IL-1β, IL-6, IL-12, IL-23, COX-2, iNOS, and adhesion molecules [20]. The recognition of LPS or DAMPs activates an essential PRR, namely TLR4.

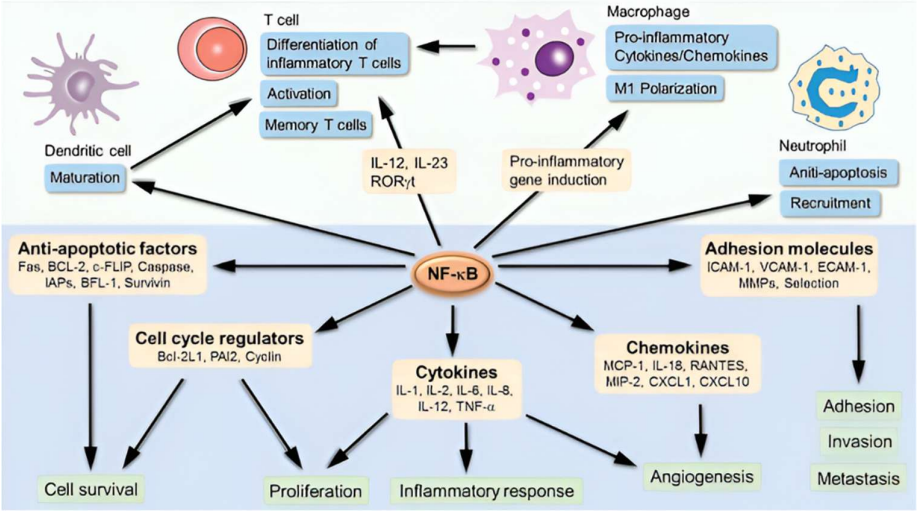

Fig. 3. Comprehensive overview of Nrf2 regulation mechanisms including Keap1-dependent ubiquitination, kinase-mediated phosphorylation (GSK-3β, PKC, CK2, PERK, JNK1, ERK2), autophagic Keap1 degradation, and nuclear ARE-driven transcription of cytoprotective genes.[32]

These extracts of B. pinnatum appear to act at both ends of this spectrum. Pretreatment with HEBP was effective in reducing the immunoreactivity of NF-κB p65 and associated cytokine production in both the DNBS and DSS colitis studies due to prevention of an increase in TLR-4 mRNA in the colon [20].

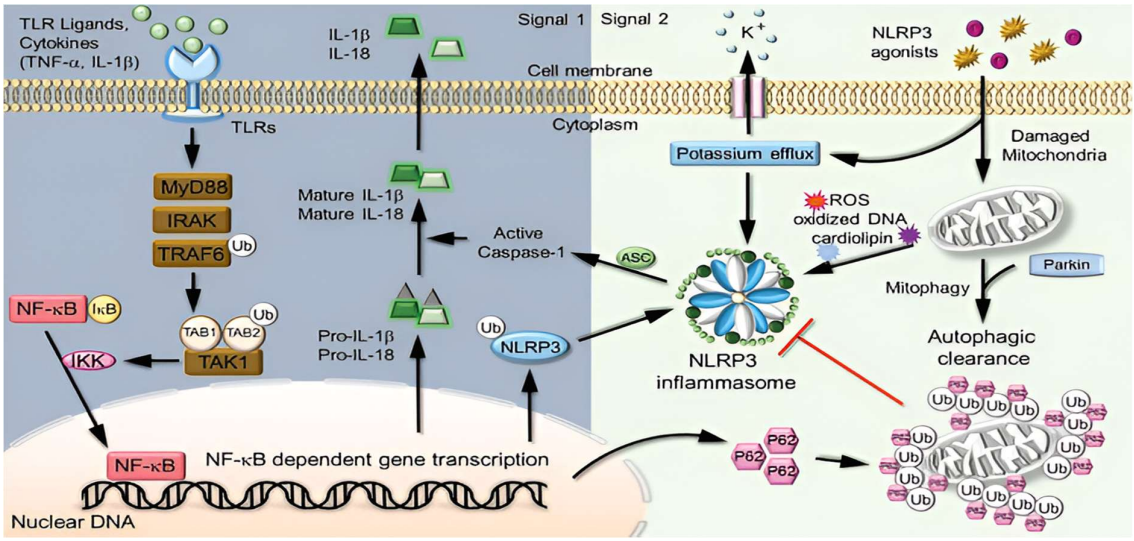

Fig. 4. Canonical Wnt/β-catenin signaling cascade showing receptor activation, destruction complex regulation, β-catenin stabilization, and nuclear co-activator recruitment, with annotated pharmacological inhibitors at each level.[27]

Inhibition of TNF-α, IL-1β, elevation of IL-10, and downregulation of COX-2 and NF-κB p65 in the study on the chronic gastric ulcer showed effects of the leaf extract of B. pinnatum [9]. The NF-κB inhibition is directly connected to its anticancer potential since cancer cell death through apoptosis results from blocking the NF-κB-mediated signaling [27]. The above effects are attributed to the following compounds: phenolic acids such as gallic acid, caffeic acid, and p-coumaric acid; flavonoids, including quercetin and kaempferol glycosides; and bufadienolides, although comparative studies have not been done on their relative contribution to these activities [9], [29].

C. Wnt/β-Catenin Pathway

Wnt/β catenin signaling is essential for both stem cell maintenance and colorectal tumorigenesis.The destruction complex (Axin – APC– GSK3β– CK1) phosphorylates cytoplasmic βcatenin in the absence of Wnt ligand, directing it toward proteasomal brea kdown.When Wnt binds to Frizzled/LRP- 5/6, Dishevelled sequesters GSK3β, allowing β- catenin to accumulate and translocat e to the nucleus, where it binds TCF/LEF to activate target genes linked to proliferation, such as cyclin D1 and c-Myc [27].

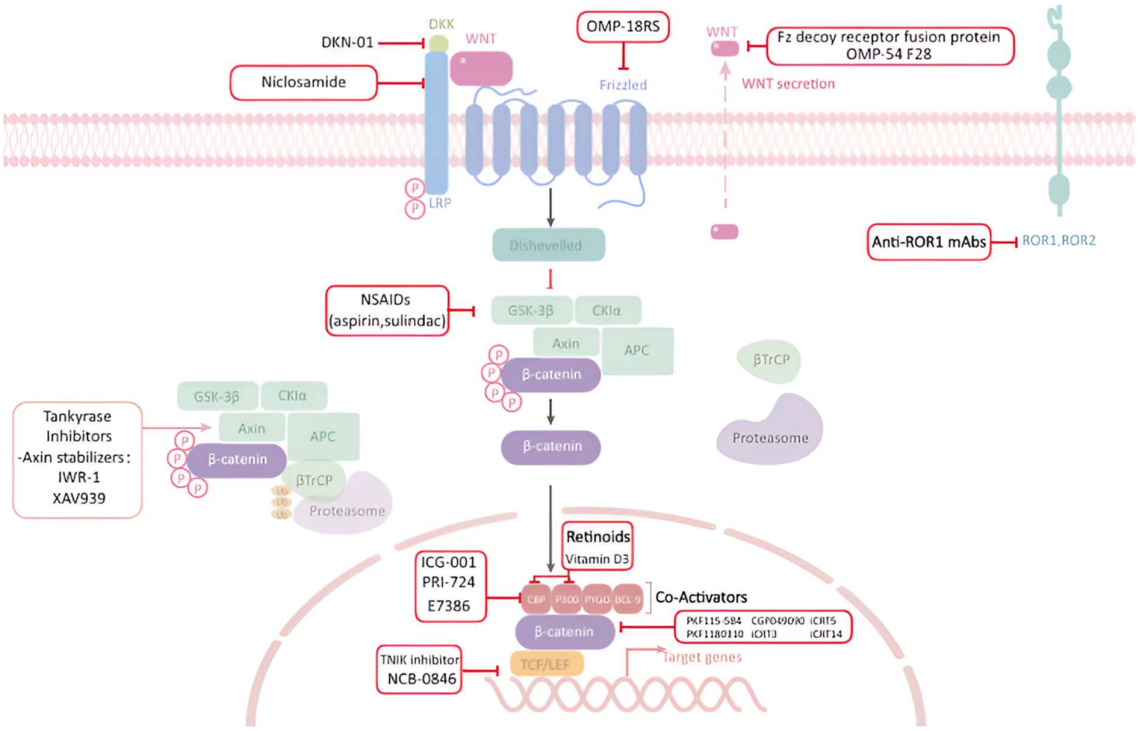

Fig. 5. NF-κB and NLRP3 inflammasome activation pathways: TLR-mediated Signal 1 drives NF-κB-dependent gene transcription, while Signal 2 stimuli (potassium efflux, ROS, damaged mitochondria) converge on NLRP3 inflammasome assembly, caspase-1 activation, and IL-1β/IL-18 maturation.[33]

Components of B. pinnatum appear to block this pathway at different points. Gallic acid has been reported to inhibit β-catenin at the mRNA and protein level, upregulating E-cadherin and Bax in xenograft models and downregulating VEGF, Oct3/4, survivin, and CCND1 in hepatocellular carcinoma cells [27]. Quercetin suppressed the nuclear translocation of β-catenin in human teratocarcinoma NT2/D1 cells. The present research suggests that quercetin up regulates Sirtuin 6 which decreases FZD4 transcripts and inhibits β-catenin accumulation [27]. Hernández-Caballero et al. (2022) showed that kaempferol induces DACT2 expression in HCT116, HT29 and YB5 colorectal cells by inhibition of DNMT1/DNMT3b, which downregulates nuclear β-catenin and inhibits Wnt pathway. Limitation: The effects of B. pinnatum on Wnt/β-catenin signaling have not been directly tested in an in vivo study, which is a major gap in future xenograft validation.

D. Nrf2 Pathway

The Nrf2/Keap1 axis is the canonical cytoprotective pathway. Under normal conditions, Keap1 traps Nrf2 and targets it for degradation by the ubiquitin-proteasome system. Under oxidative stress, the cysteine residues of Keap1 are oxidized. This releases Nrf2, which then moves to the nucleus, dimerizes with small Maf proteins, and binds antioxidant response elements. This process induces the transcription of phase II enzymes such as HO-1, NQO1, GST, GCLC, and GCLM [27]. The “Nrf2 paradox” is that while Nrf2 protects normal cells from oxidative damage, constitutive Nrf2 activation in cancer cells confers chemoresistance and pro-survival benefits.

Flavonoids and phenolic acids in B. pinnatum appear to preferentially activate Nrf2 in healthy tissue, while allowing ROS to accumulate in cancerous cells. Caffeic and p-coumaric acids phosphorylate ERK to prevent oxidative damage, which promotes Nrf2 nuclear translocation and the induction of HO-1, GCLC, and GCLM in HepG2 cells [27]. In neuroblastoma cells, quercetin inhibits Keap1, enhances nuclear Nrf2 localization, improves ARE binding, upregulates NQO1 transcription, decreases Keap1 ubiquitination, and induces HO-1 and NOS1. Kaempferol also acts as a Nrf2 activator in a similar way [27]. In addition, the same flavonoids (quercetin in A549 cells and caffeic acid in ovarian A2780 cells) enhance ROS-mediated apoptosis, highlighting the dual roles of these compounds depending on the context [25], [27]. This contradiction places B. pinnatum in the situation that Nrf2 regulation has pro anti-inflammatory and antioxidant effects in normal tissue, while the ROS spike, specific for cancer cells, preferably causes apoptosis in transformed cells. B. pinnatum has not yet been clinically tested for this indication, but the clinical relevance is supported by confirmed Nrf2-targeted anticancer techniques.

Pathway	Compound	Specific Molecular Target / Node Affected	Direction of Effect	Cell Line or Model System Used	Downstream Effect	Citation
NF-κB–TLR4	Hydroethanolic *B. pinnatum* leaf extract (flavonoid-rich)	Toll-like receptor 4	Downregulation	Rats and mice — DSS- / acetic-acid-induced colitis (in vivo) + in vitro inflamed intestinal cells	Reduced TNF-α, IL-1β, IL-6, COX-2, TFF-3 and iNOS expression in colonic mucosa; restored intestinal epithelial barrier	[20]
NF-κB–TLR4	*B. pinnatum* leaf press juice — flavonoid glycosides (quercetin, myricetin, kaempferol, diosmetin derivatives)	Intracellular Ca^{2+} signalling downstream of oxytocin receptor	Suppression (inhibition)	hTERT-C3 human myometrial cells	Attenuated OT-induced inflammatory signalling, supporting tocolytic activity	[34]
NF-κB–TLR4	Bufadienolide-enriched fraction of *B. pinnatum* leaf press juice; bersaldegenin-1,3,5-acetate; bryophyllin A; bersaldegenin-3-acetate (bersaldegenin-1-acetate inactive)	NF-κB activation; induced COX-2 expression	Downregulation of OT-induced NF-κB activation and COX-2 mRNA / protein	hTERT-C3 human myometrial cells; confirmed ex vivo in human myometrium bath model	Reduced prostaglandin $F_2\alpha$-driven uterine contractility; effect was not attributable to cytotoxicity	[35]
NF-κB–TLR4	Quercetin 3-O-α-L-arabinopyranosyl-(1→2)-O-α-L-rhamnopyranoside (Bp1; major compound, 33.12 ± 0.06 mg/g) + kaempferol glycoside (Bp2; 3.98 mg/g) + quercitrin (Bp3; 4.26 mg/g)	NF-κB (p65) and COX-2 expression in gastric mucosa	Downregulation of NF-κB p65 and COX-2; decreased IL-1β, TNF-α, MPO activity; increased IL-10	Rats — acetic-acid-induced chronic gastric ulcer (in vivo)	Gastric mucosal healing, restored antioxidant defence (↑ GSH, ↓ MDA, modulated SOD)	[9]
NF-κB–TLR4 (pathway context)	Kaempferol (general flavonoid class;	LPS → TLR4 → NF-κB signalling	Inhibition of LPS-TLR4-NF-κB axis	Dextran sulfate sodium-induced colitis mice	Restored gut microbiota; alleviated	[36]

	B. pinnatum-derived)				weight loss, diarrhoea, colon shortening	
NF-κB–TLR4 (pathway context)	Naringenin (comparison; TLR4/NF-κB axis)	TLR4/NF-κB luciferase	Inhibition of TNF-α-induced NF-κB activity	HT-29 human colon cells; DSS mice	Ameliorated experimental colitis	[36]
PI3K/AKT/mTOR (pathway context)	Quercetin (representative *B. pinnatum* flavonoid)	PI3K / Nrf2-mediated oxidative stress; mTOR in autophagy	Modulation	Multiple liver-disease models (steatosis, hepatitis, fibrosis, HCC)	Reduced inflammation, oxidative stress, apoptosis and proliferation in hepatocytes	[33]
PI3K/AKT/mTOR (pathway context)	Biflavonoids (general plant class; included for pathway-mapping)	PI3Kα and mTOR catalytic sites	Dual inhibition of PI3Kα and mTOR (chiral / atropisomerism-dependent binding)	In silico docking	Suggests achievable dual PI3Kα/mTOR inhibition for cancers with hyperactive pathway	[33]
Wnt/β-catenin	Quercetin (representative *B. pinnatum* flavonoid)	hTERT, MEK1/ERK1/2, Notch, Wnt/β-catenin signalling	Inhibition of cancer-proliferative Wnt/β-catenin signalling in HCC	Liver cancer cellular models	Inhibited hepatocellular carcinoma cell proliferation and metastasis	[33]
Wnt/β-catenin	*B. pinnatum* methanolic / ethanolic extracts containing bryophyllin A + β-sitosterol + quercetin + morin	Pancreatic / hepatic pathway nodes (PI3K, VEGFR2, IGFR, C-KIT, RET, c-Met, MEK, PDGFR)	Modulation (model-dependent)	HCT116 colorectal cells; HepG2 cells; docking models	In silico binding supports chemopreventive applications in colorectal / hepatic neoplasia	[37]
Wnt/β-catenin (pathway context)	Cardiac glycosides / flavonoid classes broadly — modulates Wnt cross-talk with ROS / Nrf2	Wnt pathway and oxidative-stress interplay	Modulation (compound- and model-specific)	Various cancer, stroke, ischemia, bone, kidney and regeneration models	Wnts modulation reshaped by ROS and vice versa in many models	[31]
Nrf2–Keap1	Quercetin (a *B. pinnatum* flavonoid)	Keap1 (cysteine electrophile sensors); Nrf2 nuclear translocation; downstream	Increase (Nrf2 dissociated from Keap1, translocated into nucleus → ARE-	E47 rat hepatocyte-like cells exposed to ethanol oxidative stress; multiple liver disease models	Hepatoprotection; antioxidant and anti-inflammatory response	[5], [30], [33]

		ARE genes (HO-1, NQO1)	driven gene induction)			
Nrf2–Keap1	*B. pinnatum* leaf hydroalcoholic extract (contains Bp1 + Bp2 + Bp3 flavonoids)	Glutathione, superoxide dismutase, malondialdehyde	Increase in GSH; decrease in MDA; modulated SOD	Rats — chronic acetic-acid gastric ulcer	Restored mucosal antioxidant defence	[9]
Nrf2–Keap1 (pathway context)	Flavonoids broadly (incl. quercetin) modulating Nrf2	keap1-Nrf2 axis; downstream HO-1, NQO-1	Negative regulation of liver-disease-promoting genes; increase in ARE target expression	Hepatocyte / liver disease in vivo/in vitro models	Alleviation of alcoholic liver disease, cirrhosis, fibrosis	[5], [30]
Nrf2–Keap1 (pathway context)	Wnt-Nrf2 cross-talk via GSK3β	Keap1, GSK3β, Nrf2	Reciprocal regulation (Wnt suppression reduces Nrf2; GSK3β inhibition restores Nrf2)	ARPE-19 retinal pigment epithelial cells; apoB100 mice	Implicates Wnt-Nrf2 coupling in chronic oxidative stress; notes chronic stress keeps Nrf2 trapped on Keap1	[32]
Apoptosis / cell-cycle (linked to NF-κB and p53 hubs)	Aqueous *B. pinnatum* leaf extract (flavonoid + bufadienolide constituents — quercetin, morin, β-sitosterol validated by HPLC-ESI/MS + GC-MS)	p53; CASPASE-3; BAX; BCL-2; ROS production	Upregulation of p53 ($p < 0.0001$), BAX ($p = 0.0252$), CASPASE3 ($p < 0.0001$); downregulation of BCL2 ($p = 0.0058$); 10× and 5.5× increase in intracellular ROS; G2/M cell-cycle arrest	HCT116 human colorectal cancer cells in vitro + STITCH in silico + molecular docking against p53/BAX/CASP3/BCL2	p53-dependent apoptosis in colorectal cancer	[37]
Apoptosis (Bcl-2 family hub)	Aqueous *B. pinnatum* extract	Bax, p53, Caspase 3 (pro-apoptotic); Bcl-2, Bcl-w (anti-apoptotic)	Upregulation of Bax, p53, Caspase 3; downregulation of Bcl-2 and Bcl-w	U87-MG glioblastoma cells	86 ± 6% apoptosis at 1 mg/mL; 85 ± 4% at 2 mg/mL (similar to 1 μM staurosporine positive control)	[32], [37]
Apoptosis (Bcl-2 family hub)	Aqueous *B. pinnatum* extract	Pro-apoptotic: Bad, Bax, p27, p53; anti-	Upregulation of Bad, Bax, p27, p53;	BxPC-3 and PANC-1 pancreatic adenocarcinoma cells	74% → 90% apoptosis after 2 h (1.5–3.0 mg	[37]

		apoptotic: Bcl-2, IGF-I, p21	downregulation of Bcl-2, IGF-I, p21		extract); up to 96.5 ± 0.5% in PANC-1	
Apoptosis (Bcl-2 family hub)	*B. pinnata* leaf extract (NMR + HPTLC characterized "fraction F4")	Bcl-2, Bax; procaspase-3; PARP-1	Decrease in Bcl-2; increase in Bax; cleavage of procaspase-3 and PARP-1 (delayed until 24 h)	HeLa human cervical cancer cells	Apoptosis via mitochondrial pathway; caspase-3 activation as a late event	[26]
Apoptosis (related)	AgNPs bio-fabricated using *B. pinnatum* leaf extract	Bcl-2; Bax; caspases 3, 8, 9	AgNP-mediated Bcl-2 downregulation, Bax upregulation	HeLa cervical cancer cells (and Allium assay for cytotoxicity)	DNA-dependent protein kinase is also downregulated — DNA damage accumulation	[38]
PDE4B (anti-inflammatory, pathway context)	Quercetin 3-O-α-L-arabinopyranosyl-(1→2)-O-α-L-rhamnopyranoside (Bp1; major *B. pinnatum* flavonoid)	Phosphodiesterase 4B (PDE4B)	Selective inhibition over PDE4A (in silico target-fishing, in vitro enzymatic inhibition, molecular dynamics)	In vitro PDE4 enzymatic inhibition	Proposed lead template for selective PDE4B blockers for inflammatory disease	[39]
MAPK / oxytocin (pathway-context, OT-induced myometrial signalling)	Bufadienolide-enriched fraction; bryophyllin A; bersaldegenin-1,3,5-acetate; bersaldegenin-3-acetate	MAPK activation; intracellular Ca^{2+}; extracellular matrix proteins	Reduction of OT-induced MAPK activation and Ca^{2+} entry; decreased ECM protein expression	hTERT-C3 myometrial cells; ex vivo human myometrium organ bath	Suppressed uterine contractility; reduced prostaglandin production	[34], [35]

TABLE 3: LISTS THE PHYTOCONSTITUENTS OF B. PINNATUM AND THEIR CORRESPONDING MOLECULAR TARGETS WITHIN THE PI3K/AKT, NF-ΚB/TLR4, WNT/B-CATENIN, AND NRF2 SIGNALING PATHWAYS.

VI. NETWORK PHARMACOLOGY AND MOLECULAR DOCKING

Network pharmacology includes target prediction, protein-protein interaction mapping, pathway enrichment, and molecular docking in the case of Bryophyllum pinnatum (Kalanchoe pinnata). Halayal et al. conducted SwissTargetPrediction-based target prediction, constructed protein-protein interaction networks with STRING 12.0, made compound-target-pathway mapping in Cytoscape 3.10.1, retrieved degree, betweenness, and closeness centrality, and performed GO/KEGG enrichment [10]. Protein-ligand interaction energies were calculated by AutoDock Tools in Discovery Studio 2018 with protein structures PDB IDs 3RX2, 1UOK, 1X70, and 4W93 [10]. In other studies regarding B. pinnatum, researchers have used Chimera 13.1 for three-dimensional visualization, AutoDock Vina in combination with LigPlus for amino acid mapping, Molinspiration for drug-likeness assessment, and pkCSM for ADMET prediction [7], [39], [40]. To identify a selective PDE4B inhibitor from B. pinnatum, Lourenço et al. further integrated target fishing with RMSD-based molecular dynamics [39].

Luteolin exhibited the most potent binding affinity (−10 kcal/mol) for antidiabetic targets, notably superior to acarbose (−7.5 kcal/mol) [10], through hydrogen bonds with Asp43, Tyr48, Lys77, Tyr209, Leu212, and Ser214, hydrophobic interactions with

Trp20, Tyr209, and Lys262, and π-stacking with Tyr209 [10]. Friedelin docked α-amylase (AMY2A) through hydrogen bonds with Tyr58, Ile61, Glu86, Lys87, Val88, Asn92, and Arg111, salt bridges with Lys87 and Arg111, and π-stacking with Phe209, yielding a docking score of −9.4 kcal/mol compared to acarbose (−7.0 kcal/mol). Molecular dynamics analysis demonstrated radius-of-gyration stability of 2.35 nm versus 2.38 nm for acarbose [10]. Friedelin also bound DPP4 at −8.7 kcal/mol via His757 and Gln761, while isorhamnetin-3-O-rutinoside achieved a binding score of −8.0 kcal/mol compared with acarbose at −7.9 kcal/mol, mediated through Tyr58, Ile59, Glu86, Lys87, Val88, Asn92, and Arg111, salt bridges with Lys307 and Arg309, and π-stacking with Phe209. KEGG enrichment of the broader network identified PPAR signaling, PI3K-Akt, neuroactive ligand-receptor interaction, and folate biosynthesis pathways as significantly enriched [10].

For antiviral applications, Souza et al. performed 264 docking simulations involving 66 B. pinnatum constituents against SARS-CoV-2 targets — Spike, ACE2, Spike/ACE2 complex, and Mpro — with 21 complexes demonstrating binding energies below −8.9 kcal/mol [7]. Rutin, astragalin, and luteolin interacted with the spike protein at Arg1000, Tyr741, Phe855, Met740, and Thr573, with binding energies of −9.1, −9.0, and −9.0 kcal/mol, respectively, whereas kaempferitrin, myricitrin, and diosmin interacted with Mpro via His41, Cys145, Gly143, and Gln189 [7]. Notably, kaempferitrin, myricitrin, and diosmin demonstrated superior docking scores relative to remdesivir (−7.9 kcal/mol) and paxlovid (−7.6 kcal/mol) at the Mpro target. [7] additionally reported the highest spike protein affinity for bryotoxin B (−9.9 kcal/mol) and the highest ACE2 affinity for diosmin (−9.0 to −9.4 kcal/mol). Aurora et al. further extended this analysis using CABS-flex 2.0 molecular dynamics simulations for the following compounds evaluated against gamma-variant targets: rutin, astragalin, friedelin, luteolin, kaempferol, quercetin, cyanidin, taxifolin, and narcissin. Rutin was identified as a non-competitive inhibitor of Mpro with favorable ADMET-QSAR safety profiles, although contact stability was reported as suboptimal [5], [41].

Compound	Target Protein	Binding Energy (as stated)	Reference / Comparator Drug and Its Binding Energy	Key Interacting Residues	Docking / Simulation Software Used	Molecular Dynamics (yes/no + duration)	**Citation**
3,5-Dihydroxybenzoic acid	Dipeptidyl peptidase-4 / DPP-4 (PDB 5Y7K)	−5.623 kcal/mol (highest; CH_2Cl_2 solvent)	No standard inhibitor docked for direct comparison	—	Schröding er software suite	No MD reported	[3]
3,4-Didehydro-N_4-deethylbrinzolamide	Dipeptidyl peptidase-4 / DPP-4 (PDB 5Y7K)	−4.91 kcal/mol (second-highest; CH_3OH solvent)	Not compared numerically	—	Schröding er software suite	No MD reported	[3]
Luteolin	Aldose reductase	−10 kcal/mol	Acarbose (standard); comparative residue panel in same paper	TRP20, TYR209, LYS262 (hydrophobic); ASP43, TYR48, LYS77, TYR209, LEU212, SER214; TYR209 (π-stacking; salt bridge)	AutoDock Vina + Discovery Studio-like workflow	No MD reported in this target row	[10]

Friedelin	Alpha-amylase (AMY2A)	−9.4 kcal/mol	Acarbose (standard inhibitor; binding energy in same paper)	TYR58, ILE61, GLU86, LYS87, VAL88, ASN92, ARG111 (hydrophobic); LYS87, ARG111; PHE209 (π-stacking)	AutoDock Vina + Discovery Studio-like workflow	Yes — 200 ns MD simulation performed (alpha-amylase–FRI vs. alpha-amylase–STD/acarbose; SASA, RG, H-bond stability assessed)	[10]
Acarbose (standard)	Alpha-amylase (AMY2A)	Visualised in 2D interaction panel of same paper; no separate numeric value reported	Reference compound	Same panel as friedelin	AutoDock Vina + Discovery Studio-like workflow	Yes — 200 ns MD simulation performed	[10]
Friedelin	DPP-4	−8.7 kcal/mol	Acarbose visualized for same target	HIS757, GLN761	AutoDock Vina	No MD reported	[10]
Isorhamnetin-3-O-rutinoside	Alpha-glucosidase	−8.0 kcal/mol	Standard comparator shown in 2D panel	TYR58, ILE59, GLU86, LYS87, VAL88, ASN92, ARG111, LYS307 (hydrophobic); ARG309; PHE209 (π-stacking)	AutoDock Vina	No MD reported	[10]
Bryophyllin A	PI3K	Highest binding among 8 hepatocarcinogenic targets (exact kcal/mol not in excerpt)	β-sitosterol; semiquantitative comparison "strongly interacted with PI3K than the other proteins"	—	CB-Dock; UCSF Chimera X for optimisation	No MD reported	[26]
β-Sitosterol	c-Met	Stronger interaction vs. c-Met than other targets	Bryophyllin A; "β-sitosterol showed	—	CB-Dock; UCSF	No MD reported	[42]

		(exact kcal/mol not in excerpt)	stronger interaction with C-met"		Chimera X		
Bryophyllin A	VEGFR2, IGFR, C-KIT, RET, PI3K, c-Met, MEK-inhibitor, PDGFR (panel)	Lower than PI3K score (full panel of 8 docking runs)	β-sitosterol as comparator	—	CB-Dock; UCSF Chimera X	No MD reported	[26]
β-Sitosterol	VEGFR2, IGFR, C-KIT, RET, PI3K, MEK-inhibitor, PDGFR (panel)	Lower than c-Met score (full panel of 8 docking runs)	Bryophyllin A as comparator	—	CB-Dock; UCSF Chimera X	No MD reported	[42]
Quercetin	p53 / BAX / CASP3 / BCL2 (network-derived HCT116 target set)	Strong binding reported (exact kcal/mol not in excerpt)	Morin, β-sitosterol as comparators within B. pinnatum leaf extract	—	STITCH (network) + molecular docking (software not stated)	No MD reported	[37]
Morin	p53 / BAX / CASP3 / BCL2 (HCT116 target set)	Strong binding reported (exact kcal/mol not in excerpt)	Quercetin, β-sitosterol (same panel)	—	STITCH + molecular docking	No MD reported	[37]
β-Sitosterol	p53 / BAX / CASP3 / BCL2 (HCT116 target set)	Strong binding reported (exact kcal/mol not in excerpt)	Quercetin, morin (same panel)	—	STITCH + molecular docking	No MD reported	[37]
Bryophyllin B	Interleukin-6 / IL-6	"Strongest affinity" — exact kcal/mol not in available excerpt	Bryotoxin A (cytokine panel); not numerically compared	—	PyRx 9.5; visualisation in PyMOL + Discovery Studio	No MD reported	[43]
Bryotoxin A	Gly-ACE (glycosylated ACE; PDB ID not stated)	"Highest binding" — exact kcal/mol not in available excerpt	Bryophyllin B (cytokine panel); not numerically compared	—	PyRx 9.5; visualisation in PyMOL + Discovery Studio	No MD reported	[43]
Bryotoxin A	TNF-α	"Highest binding" — exact kcal/mol not in available excerpt	Bryophyllin B (cytokine panel); not numerically compared	—	PyRx 9.5; visualisation in PyMOL + Discovery Studio	No MD reported	[43]
Bryotoxin B	SARS-CoV-2 Spike glycoprotein (PDB 6VXX)	−9.9 kcal/mol (highest among 66 compounds; 21	No direct reference drug	—	AutoDock Tools 1.5.6 + AutoDock	No MD reported	[7]

		compounds < −8.9 kcal/mol)	numerically in the paper		Vina (LigPlus for residues; Chimera v.13.1 for 3D)		
β-Amyrin acetate	SARS-CoV-2 Spike / Mpro / 1R42 (PDB 6VXX, 6LU7, 1R42; multiple proteins)	Binding < −8.9 kcal/mol (top 21 compounds)	Bryotoxin B (top binder); no numeric standard in source	—	AutoDock Tools 1.5.6 + AutoDock Vina	No MD reported	[7]
Diosmin	SARS-CoV-2 Spike / Mpro / 1R42 (PDB 6VXX, 6LU7, 1R42)	Binding < −8.9 kcal/mol (top 21 compounds)	Bryotoxin B (top binder); no numeric standard in source	—	AutoDock Tools 1.5.6 + AutoDock Vina	No MD reported	[7]
3,6-Diglucosylapigenin	SARS-CoV-2 3Clpro / Mpro	−10.59 kJ/mol	Boceprevir (standard 3CLpro inhibitor; reported as "similar") — exact comparator energy not in excerpt	Active site residues of 3CLpro (specific residues not in available excerpt)	Quikprop software used for ADME-tox; docking software not separately named	Yes — MD simulation performed (RMSF, SASA, number of H-bonds analysed; ligand escape from far-from-active-site residues observed)	[5], [7]
Bryophyllin B	Vespula vulgaris allergen proteins (Ves V1: phospholipase A1; Ves V2: hyaluronoglucosaminidase; Ves V5: antigen 5)	−9.6 kcal/mol (consistent across all three allergen targets)	Bryotoxin A highest; not numerically compared	—	Docking software named in same paper (not in available excerpt)	Yes — 100 ns MD simulation performed (RMSD, RMSF, RG, protein–ligand contacts analysed)	[44]
Bryotoxin A	Vespula vulgaris allergen proteins (Ves V1, Ves V2, Ves V5)	−10.0 kcal/mol (consistent across all three allergen targets)	Bryophyllin B as comparator	—	Docking software (not in available excerpt)	Yes — 100 ns MD simulation performed	[44]
24-Ethyl-desmosterol	Aedes aegypti larvicidal target (vector; exact protein not stated)	−10.6 kcal/mol (best against vector)	Clerosterol (second-best)	—	Docking software (not in	Yes — 150 ns MD simulation performed	[45]

					available excerpt)		
Clerosterol	Aedes aegypti larvicidal target	−10.5 kcal/mol	24-Ethyl-desmosterol	—	Docking software (not in available excerpt)	Yes — 150 ns MD simulation performed	[45]
Taraxasterol	Dengue NS5 polymerase	−9.7 kcal/mol (best against NS5)	Bryophynol (second-best for same target)	—	Docking software (not in available excerpt)	Yes — 150 ns MD simulation performed	[45]
Bryophynol	Dengue NS5 polymerase	−9.6 kcal/mol	Taraxasterol	—	Docking software (not in available excerpt)	Yes — 150 ns MD simulation performed	[45]
25-Methylstigmast-24-enol	Dengue NS2B/NS3 protease	−8.9 kcal/mol (best against protease)	Clerosterol (tied-best)	—	Docking software (not in available excerpt)	Yes — 150 ns MD simulation performed	[45]
Clerosterol	Dengue NS2B/NS3 protease	−8.9 kcal/mol (tied-best)	25-Methylstigmast-24-enol	—	Docking software (not in available excerpt)	Yes — 150 ns MD simulation performed	[45]
Quercetin 3-O-α-L-arabinopyranosyl-(1→2)-O-α-L-rhamnopyranoside	PDE4B (phosphodiesterase 4B; PDB ID not stated)	Selective inhibition over PDE4A (specific kcal/mol not in available excerpt)	Rolipram-class PDE4 inhibitors (implied standard)	—	Target-fishing (inverse virtual screening) + molecular dynamics	Yes — MD simulations performed (interaction profiling only; specific ns not in excerpt)	[39]
Astragalin (kaempferol 3-O-glucoside)	Mineralocorticoid receptor (MR; PDB 5L7E)	−9.209 kcal/mol (closest to native ligand)	Native ligand: −9.691 kcal/mol	Hydrogen bonds with key residues; hydrophobic interactions (specific residues not in available excerpt)	DockThor-equivalent workflow (AutoDock Vina-type; software in source)	No MD reported	[46]

Patuletin	Mineralocorticoid receptor (MR; PDB 5L7E)	−8.572 kcal/mol	Native ligand −9.691 kcal/mol	—	Same workflow as above	No MD reported	[46]
Pinoresinol	Acetylcholinesterase (AChE; PDB 7E3H)	−10.281 kcal/mol (best among B. pinnatum compounds); MM/GBSA ΔGbind = −35.82 kcal/mol	Selegiline −7.416 kcal/mol, MM/GBSA −24.89; Rasagiline −7.161, MM/GBSA −21.48	—	Docking + MM/GBSA scoring (software not in available excerpt); MAO-B structure 4A7A in same paper	No MD reported	[47]
Chrysin	Acetylcholinesterase (AChE; PDB 7E3H)	−9.214 kcal/mol; MM/GBSA ΔGbind = −18.54 kcal/mol	Selegiline / Rasagiline comparators	—	Same workflow as pinoresinol	No MD reported	[47]
Anthrone	Acetylcholinesterase (AChE; PDB 7E3H)	−8.748 kcal/mol; MM/GBSA ΔGbind = −33.50 kcal/mol	Selegiline / Rasagiline	—	Same workflow	No MD reported	[47]
Ferulic acid	Acetylcholinesterase (AChE; PDB 7E3H)	−7.939 kcal/mol; MM/GBSA ΔGbind = −35.93 kcal/mol	Selegiline / Rasagiline	—	Same workflow	No MD reported	[47]
Selegiline (standard)	Monoamine oxidase-B (MAO-B; PDB 4A7A)	−7.416 kcal/mol; MM/GBSA ΔGbind = −24.89 kcal/mol	Reference MAO-B inhibitor	—	Same docking + MM/GBSA workflow	No MD reported	[47]
Rasagiline (standard)	Monoamine oxidase-B (MAO-B; PDB 4A7A)	−7.161 kcal/mol; MM/GBSA ΔGbind = −21.48 kcal/mol	Reference MAO-B inhibitor	—	Same workflow	No MD reported	[47]

TABLE 4: PRESENTS BINDING ENERGIES OF *B. PINNATUM* COMPOUNDS AGAINST PHARMACOLOGICAL AND SARS-COV-2-RELATED TARGETS, WITH REFERENCE-DRUG COMPARISONS WHERE AVAILABLE.

The computational approaches described above are inherently subject to methodological limitations. Molecular dynamics simulations only partially address the constraints of static in silico docking, which presupposes a rigid lock-and-key binding model and does not account for protein conformational flexibility, explicit solvent dynamics, or entropic contributions to binding

free energy [39], [41]. Furthermore, docking scores do not incorporate pharmacokinetic parameters such as oral bioavailability, plasma protein binding, central nervous system penetration, or volume of distribution; pkCSM-generated ADMET predictions themselves constitute computational models with associated uncertainty [7]. With respect to pharmacokinetic profiles, lipophilic constituents such as friedelin and pseudotaraxasterol (logBB ≈ +0.7) demonstrated blood-brain barrier penetration capacity, whereas astragalin (VDss = −0.498 log L/kg) and rutin (logBB = −2.556) raised concerns regarding the capacity of unbound drug to attain therapeutically relevant concentrations at target tissues [7]. Accordingly, the translational pipeline from computational docking to clinical application must necessarily encompass molecular dynamics refinement, comprehensive ADMET profiling, and ultimately in vitro enzymatic and cellular assay validation, followed by in vivo pharmacokinetic studies, before substantive therapeutic claims can be advanced [5], [7].

VII. SAFETY AND TOXICITY PROFILE

A. Bufadienolide Cardiotoxicity

B. pinnatum synthesizes bufadienolides — including bryophyllin A and B, bersaldegenin-1,3,5-orthoacetate, and its 1- and 3-acetate derivatives — that are structurally and pharmacologically analogous to digitalis-type cardiac glycosides [1], [6]. Although these compounds enhance myocardial contractility, they concurrently elevate the risk of arrhythmia and conduction disturbances, necessitating rigorous assessment of the therapeutic window prior to clinical application [2], [5], [48]. Cardiotoxicity has been documented in livestock; two calves administered 20 g/kg of floral material developed anorexia, ruminal stasis, and marked depression, with one succumbing at 9 hours from tachycardia and dyspnea and the other at 15.5 hours following the onset of diarrhea [1]. In an acute rodent toxicity experiment, methanolic leaf extract at 200 mg/kg produced 100% lethality within 24 hours, whereas no fatalities were recorded at 25 mg/kg [1]. A clinical case report from 2025 described a 63-year-old male with hypertension, a history of percutaneous transluminal coronary angioplasty (PTCA), and mild left ventricular dysfunction who experienced rapid clinical deterioration after ingesting three to four raw leaves, culminating in metabolic acidosis, sepsis, and cardiorenal syndrome[2], [48]. Importantly, toxic thresholds documented in animal models are several hundred-fold higher than the concentrations present in conventional pharmaceutical formulations of the plant [5]

B. General Toxicity Studies

No toxicological manifestations or fatalities were observed in Sprague-Dawley rats administered a maximum oral dose of 5 g/kg, nor at an intraperitoneal LD50 of 1.8 g/kg [49]. A 35-day sub-acute oral regimen of 2 g/kg per day produced no significant alterations in body weight, organ-to-body-weight ratios, fluid intake, or hematological indices relative to controls; moreover, statistically significant reductions in AST, ALP, albumin, total and conjugated bilirubin, and ALT ($p < 0.03$) were interpreted as indicative of hepatoprotection rather than hepatotoxicity [49]. The absence of neutrophilia further confirmed a lack of systemic inflammatory response [49].

In the context of anthroposophic obstetric medicine, B. pinnatum preparations were clinically well tolerated at concentrations of 5% for intravenous administration and 50% for oral tocolysis. In direct comparison with β-mimetic tocolytic agents, B. pinnatum induced substantially fewer episodes of palpitation and dyspnea. Among 14 pregnant women treated with 50% chewable tablet formulations, no clinically significant adverse events were recorded; only isolated occurrences — specifically, one case of facial exanthema and one case of suspected lactose-intolerance-associated diarrhea — were documented [1]. Collectively, these findings highlight that the risk associated with concentrated extracts and isolated bufadienolides must be contextualized within a dose-response framework, as distinct from the centuries-long record of traditional use without documented widespread adverse effects [1], [5].

C. Drug Interactions and Standardization Challenges

Flavonoids of B. pinnatum, when co-administered with conventional antidiabetic agents, appear to potentiate the glucose-lowering effect of metformin through immunomodulatory mechanisms in type II diabetes mellitus, raising the potential for hypoglycemia and additive glycemic reduction [5]. Of particular clinical concern is the shared inhibition of Na+/K+-ATPase by bufadienolides and prescription cardiac glycosides such as digitalis and digoxin, which poses a meaningful pharmacodynamic interaction risk for patients with cardiovascular comorbidities. Additionally, metabolic overlap between flavonoid pathways and the biotransformation routes of certain antiviral agents may give rise to pharmacokinetic drug interactions that warrant prospective investigation [1], [5].

From a phytochemical standardization perspective, total bufadienolide content across independently sourced batches has been reported to range from 3.78 to 40.50 mg per 100 g of dry weight, with three bersaldegenin derivatives and bryophyllin A identified

as the principal constituents and consistently higher concentrations detected in younger leaf tissue [1], [8]. Seasonal fluctuations, chemotypic variation, and inter-laboratory differences in extraction methodology collectively complicate dose definition and impede the design of reproducible clinical trials. Accordingly, the establishment of validated quantitative chemical markers, adherence to Good Manufacturing Practices, and implementation of WHO guidelines for herbal medicine standardization are considered indispensable prerequisites for ensuring consistent potency and reliable safety profiles in future phytopharmaceutical development [8], [22].

VIII. CONCLUSION AND FUTURE PERSPECTIVES

A. Summary of Evidence

Substantial experimental evidence accumulated over the past three decades substantiates the multi-target pharmacological potential of Bryophyllum pinnatum. Ethanolic leaf extracts have demonstrated selective, reactive oxygen species (ROS)-mediated cytotoxicity against HT-29 colon carcinoma cells (selectivity index = 8.4) [25] as well as p53-mediated apoptotic activity in HCT116 colorectal cancer cells [37]. Hydroethanolic preparations have been shown to attenuate colon shortening and ulceration through suppression of TLR4/NF-κB p65 expression in rodent colitis models [20], while concurrently reducing chronic gastric ulceration via coordinated inhibition of pro-inflammatory cytokines and cyclooxygenase-2 (COX-2) [50]. Aqueous and ethanolic extracts have further exhibited inhibitory activity against α-amylase and α-glucosidase at IC_{50} values comparable to those of the reference inhibitor acarbose in vitro, and produced significant hypoglycemic effects in both streptozotocin (STZ)- and alloxan-induced diabetic rodent models in vivo [51], [52].

Network pharmacology investigations have consistently identified the PI3K/AKT, Wnt/β-catenin, NF-κB, Nrf2, and PPAR signaling axes as convergent molecular targets of B. pinnatum phytoconstituents [10], [27]. Computational docking studies have further reported favorable binding energies of plant-derived compounds against SARS-CoV-2 main protease (Mpro) and spike protein targets [7]. Notwithstanding these promising findings, the preponderance of available evidence remains confined to in vitro, in silico, and rodent-based experimental paradigms, with clinical data limited to small-cohort anthroposophic tocolysis trials [1]. This disparity underscores a substantive translational gap between bench-level mechanistic evidence and bedside therapeutic application that must be systematically addressed.

B. Translational Gaps

Several critical impediments currently constrain the clinical translation of B. pinnatum bioactives. First, the absence of standardized phytochemical composition represents a foundational challenge, as total bufadienolide concentrations across independently sourced batches have been reported to range from 3.78 to 40.50 mg per 100 g of dry weight — a variability attributable to differences in geographic provenance, leaf ontogenetic stage, and harvest date — thereby complicating batch-to-batch reproducibility and dose definition [1]. Second, available mechanistic data remain largely derived from cell culture and computational models; the absence of in vivo target-validation studies employing gene knockout, siRNA silencing, or xenograft approaches substantially limits the confidence that can be placed in pathway-specific mechanistic claims [23]. Third, no Phase I or Phase II clinical trials have been registered or reported for anticancer, antidiabetic, or antiviral applications of B. pinnatum preparations [1], [6].

Fourth, bufadienolide-associated cardiotoxicity remains a principal safety concern for clinical development, as evidenced by a 2025 case report documenting fatal systemic toxicity following raw leaf ingestion in a patient with pre-existing cardiovascular disease [2], [48]. Fifth and finally, comprehensive pharmacokinetic data — encompassing oral bioavailability, plasma half-life, tissue distribution, and cytochrome P450-mediated metabolic pathways — remain largely absent for the principal flavonoid glycoside and bufadienolide constituents; rigorous ADMET profiling of these primary bioactives constitutes an indispensable prerequisite for any future clinical development program [5].

C. Future Directions

Future research efforts should be organized around a coordinated translational agenda that systematically bridges existing mechanistic evidence and clinical application. Advanced nanoformulation platforms — including liposomal systems, polymeric nanoparticles, and self-nanoemulsifying drug delivery systems (SNEDDS) — present promising opportunities to enhance the aqueous solubility, oral bioavailability, and tissue-targeted delivery of poorly soluble bufadienolides and triterpenes, while potentially narrowing their cardiac safety window through controlled-release pharmacokinetics [23], [53]. Combination pharmacotherapy exploiting synergistic interactions between B. pinnatum phytoconstituents and established anticancer agents (doxorubicin, erlotinib) or antidiabetic drugs (metformin, glibenclamide) represents a strategically valuable avenue warranting systematic in vitro and in vivo investigation [10], [27].

Molecular dynamics simulations coupled with free-energy perturbation calculations are required to validate and refine static docking predictions by accounting for protein conformational flexibility and explicit solvent dynamics [7]. Concurrently, in

vivo target validation employing conditional gene deletion or siRNA-mediated knockdown approaches, in conjunction with systematic ADMET and pharmacokinetic profiling in appropriate rodent models, will be essential to bridge mechanistic observations to physiologically relevant outcomes. Ultimately, rigorously designed, randomized, placebo-controlled clinical trials conducted in accordance with WHO guidelines for the standardization of herbal medicines represent the definitive translational endpoint required to integrate this pharmacologically versatile Crassulaceae species into the framework of evidence-based therapeutics. The breadth and depth of its ethnomedicinal heritage constitute an enduring scientific motivation for continued rigorous investigation [23], [29].

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