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Vernonia Amygdalina (Bitter Leaf) Breakthrough: Unveiling the Phytochemical and Pharmacological Power

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ABSTRACT: *Vernonia amygdalina* is a medicinal plant with a wide range of phytochemical constituents and pharmacological properties that have been extensively studied. Although traditional and scientifically proven, crude extracts are subjected to such limitations as poor stability, low bioavailability and varied therapeutic effect, which require formulation-based approaches for improving the clinical applicability of crude extracts. The objective of this review is to assess and consolidate the literature related to the formulation and combination-based development of *V. amygdalina* to various pharmaceutical and functional delivery systems. Structured literature search was retrieved from the databases such as PubMed, Google Scholar, ScienceDirect, EBSCO and Scopus with the search terms "*Vernonia amygdalina*", "formulation" and "combination formulation" and "drug delivery systems" to identify the relevant studies on the development of formulation and therapeutic application. The results revealed successful incorporation of *V. amygdalina* into several formulation systems which enhance stability, bioavailability and therapeutic efficiency. Combination formulations that were created with other plant extracts and conventional drugs showed improved antimicrobial and antidiabetic properties, indicating possible synergism. Most of the studies are still in the preclinical phase, and there are very few clinical studies, and not much research on interaction mechanisms. The therapeutic properties are mainly due to the presence of bioactive molecules like flavonoids, sesquiterpene lactones, alkaloids, and saponins which have antioxidant, antimicrobial, anti-inflammatory, and antidiabetic properties. *V. amygdalina* has a high potential as a multifunctional medicinal plant with advanced pharmaceutical and functional applications. To conclude, it is clear that additional clinical trials, formulation standardization, and interaction studies are required to further validate its therapeutic potential in the realm of evidence-based medicine.

1. INTRODUCTION

The number of people suffering from both chronic disease and infectious disease is rising and this highlights the urgency of new treatments that are safer, less expensive, and more accessible. Medicinal plants have been used for centuries and have a broad spectrum of acceptable uses and diverse pharmacological properties. They are being increasingly considered as a source of safe, inexpensive and easily available therapies. Medicinal plants continue to be a major component of health care for a large portion of the world's population due to the fact that access to conventional medical treatment is often limited. In addition, the current literature demonstrates that medicinal plants provide not just a means for individuals to receive primary health care but also serve as a valuable resource for discovering new therapeutic compounds.[1,2] Additionally, the increased interest in natural products has been motivated by concern regarding side effects, drug resistance, and the financial costs associated with the

production of synthetic drugs. Approximately, eighty percent of the population in developing nations utilize traditional forms of medicine, primarily plant based for their basic health care requirements. There appears to be a recent resurgence of interest in using natural remedies globally, due to an increase in awareness of their potential therapeutic applications and an escalation in the prevalence of chronic disease, indicating a major paradigmatic shift toward incorporating traditional forms of medicinal knowledge into current practice.[3]

The use of medicinal plants has been a key component in the development of today's pharmacotherapy. The importance of plant-derived compounds and drugs is now well known, as a significant number of currently available drugs are directly derived from plants or are inspired by plant-derived compounds. Ethnopharmacological knowledge, which has been developed over thousands of years, is crucial for identifying biologically active compounds and the knowledge that it has to offer continues to be important for drug discovery. The use of traditional knowledge along with scientific methods has helped in the conversion of herbal medicines to scientific medicine.[4,5] Advances in phytochemistry and molecular biology have also contributed to the understanding of phytochemicals obtained from plants and their mode of action and therapeutic potential.[6,7]

Vernonia amygdalina (bitter leaf) has been the medicinal plant of interest among the various medicinal plants that were studied due to its wide ethnomedicinal uses. *V. amygdalina* is one of the species of plants in the family *Asteraceae*. It is common knowledge as bitter leaf because of its bitterness and is also known as daun bismillah in Malaysia. It is a native plant of tropical Africa and has traditionally been used for a variety of illnesses, and inflammatory diseases. Herbal remedies have been transformed into scientific medicine via the application of both traditional knowledge and scientific methods. In *V. amygdalina*, phytochemicals and essential mineral elements have been identified in both the young and mature leaves; this could be the key to the medicinal properties of the plant.[8] The plant is also easily accessible and adaptable which makes it a valuable plant for further pharmaceutical study and development.[9]

Although there is a great deal of potential for medicinal plants to be used therapeutically, there are also some significant issues with using crude plant extracts directly as drugs; one major concern is that they have low bioavailability. Many of the plant-based compounds (natural products) which are contained within plants have low bioavailability as a result of poor absorption through the GI tract. Additionally, many plant-based compounds are quickly metabolized by the body so very few if any of these compounds reach the bloodstream. In addition to this, crude plant extracts may be degraded when they are exposed to oxygen and/or water for extended periods of time; as such the degradation process will result in loss of potency of the extract. Therefore, due to factors including but not limited to growth conditions, harvesting practices, processing methods, etc. crude plant extracts may contain varying levels of active ingredients. Most crude plant extracts have a large number of different chemical compounds which can interact with each other in an unpredictable manner, which adds to the problem of variable content. This makes it difficult to guarantee quality of plant-based medicines, both in terms of quality and quantity.[10,11]

On the other hand, formulation technology is now one of the most important approaches to overcome raw plant extracts inherent limitations. The main goal of drug formulation is to convert unstable and poorly absorbed plant derived drugs into stable and better absorbed and delivered drugs via proper dosage form. This may also improve the compliance of the patients by improving the taste, use and precision dosing properties of medicinal plants. Various formulations can be used to optimize the delivery of active ingredients from plants (e.g. Gels, creams, pills, capsules). Research on the use of formulation technology is becoming increasingly important as it relates to converting natural remedies that have been used traditionally to standard, clinical products.[3]

The use of numerous botanicals (i.e., the extracts from plants) in one single formula or preparation, or combined formulation, represents an emerging area of research and study regarding herbal formulations. Based upon the theory of synergism — that is, the collective action of various bioactives within a polyherbal formulation will provide increased therapeutically effective activity, bioavailability and/or reduced toxicity compared with each active compound individually — polyherbal formulations have been developed. Furthermore, the potential exists for polyherbals to modulate additional physiological pathways, thus enhancing treatment outcomes. In a similar manner to traditional medicine where combinations of herbs may be employed to achieve a desired outcome; despite the increasing interest in these polyherbal preparations, they require additional scientific validation and standardization to support their use.[12–14]

In spite of extensive investigation regarding the ethnomedicinal importance and biological characteristics of *V. amygdalina*, there are limited studies related to incorporating it into optimized pharmaceutical formulations and in combinations with other medicinal plants. Most existing studies have focused primarily upon the individual properties of *V. amygdalina*, with insufficient emphasis placed upon the development and assessment of formulations. As such, a gap exists which could be used to create new methods for developing innovative formulation approaches capable of enhancing its therapeutic value and expanding its usage within modern medicine. The objective of this current study was to create and assess formulations that contain *V. amygdalina* as a singular extract as well as in conjunction with additional plant-derived compounds. In doing so, we address limitations in using raw plant extracts while also assessing the possible advantages of using combination formulations; our ultimate goal is to assist in the advancement of botanical-based therapy and facilitate their inclusion in modern health care practices.

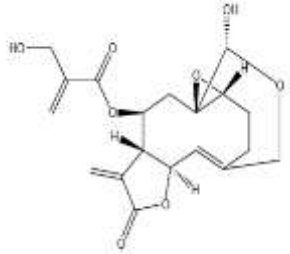
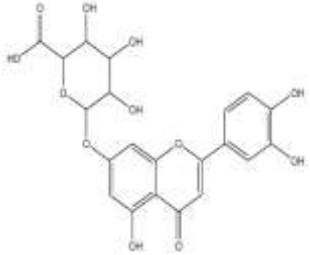
2. METHODOLOGY

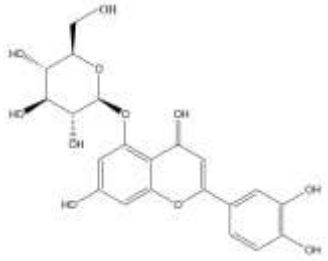
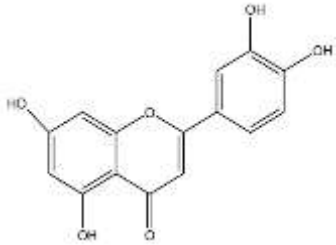
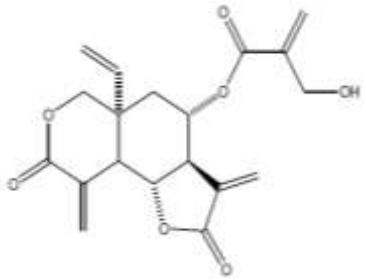
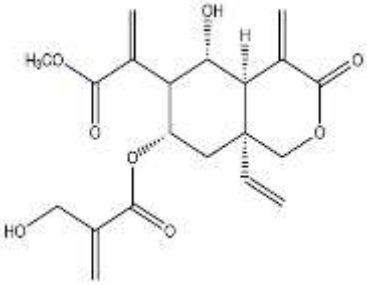
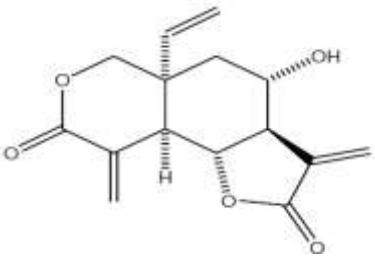
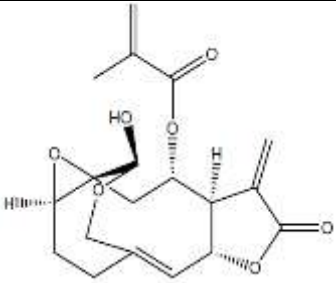
A comprehensive review of herbal formulations was conducted beginning with an extensive literature search across several databases, such as PubMed, Google Scholar, ScienceDirect, EBSCO and Scopus. The search focused on peer-reviewed articles published via keywords such as "*Vernonia amygdalina*", "phytochemical screening", "pharmacological activities", "formulation," "combination formulation,", "synergistic effect", and "drug delivery systems". Relevant publications were identified by screening their titles, abstracts, and full texts. Only studies examining the phytochemical constituents, pharmacological properties, or formulation development of *V. amygdalina* were included, whereas duplicate records and articles outside the scope of the review were omitted. The retained studies were then grouped according to their main research focus—namely, phytochemical analysis, pharmacological assessment, single-herb formulations, and combination formulations. Where reported, the experimental designs employed, including in vitro, in vivo, and clinical investigations, were also taken into account.

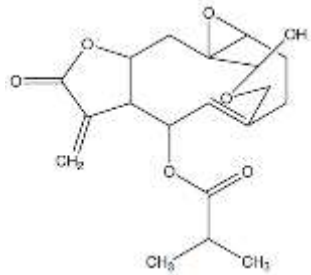
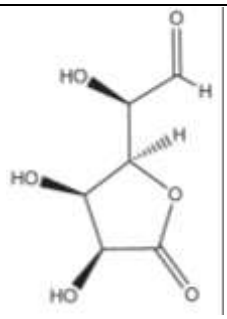
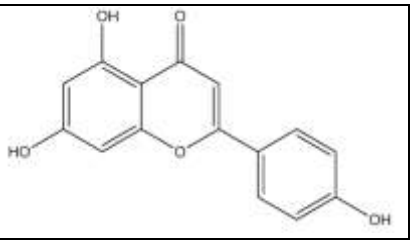
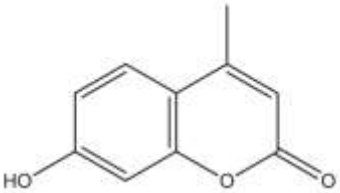
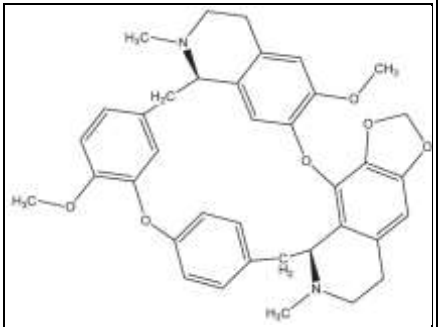
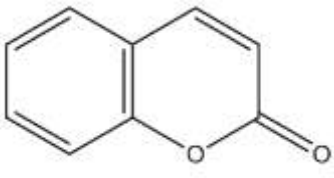
3. PHYTOCHEMISTRY OF *VERNONIA AMYGDALINA*

Phytochemicals are the bioactive compounds that have been extracted from the parts of the plant. To identify the phytochemical present in the plant, phytochemical screening will be conducted to discover the presence of secondary metabolites. A study has demonstrated the presence of saponins, flavonoids, alkaloids, steroids, tannins, triterpenoids, and cardiac glycosides from the leaves of *V. amygdalina*.[15] Additionally, according to Degu et al. (2024), other parts of the bitter leaf plant, namely roots, seeds, stems, and flowers, also contain the phytochemicals that have ethnomedicinal uses, which can be beneficial in many diseases such as jaundice, malaria, snake bites, stomachache, athlete's foot, etc.[16] These findings highlight the importance of underutilized parts of *V. amygdalina*, which are often discarded as waste, yet they exhibit various bioactive compounds and nutritional advantages. The table below shows the extracted phytochemicals from various parts of the *V. amygdalina* plant.[17,18]

Table 1. Some isolated bioactive compounds from *V. amygdalina* and its chemical structures

Isolated Bioactive Compounds	Chemical Structures
Hydroxyvernolide	
Luteolin 7-O-β-glucoroniside	

Luteolin 7-O-β -glucoside	
Luteolin	
Vernodalin	
Vernodalol	
Vernolepin	
Vernolide	

Vernomygdin	
Glucuronolactone	
Apigenin	
4-methylumbelliferone	
Cephantharin	
Courmarins	

4. PHARMACOLOGICAL PROFILE OF *VERNONIA AMYGDALINA*

4.1 Anti-inflammatory activity

A study was conducted to assess the anti-inflammatory effect of *V. amygdalina* extract by comparing it to acetylsalicylic acid. Four parts of pyridine stimulated the inflammation: one-part distilled water, five parts diethyl ether, and ten parts croton oil in diethyl ether (v/v). After six hours of application to the right ear, all animals were lightly anesthetized. Then, the ears were removed and weighed using a sensitive balance. The level of inflammatory response was calculated and compared between the study groups. The results showed that the *V. amygdalina* extract significantly reduced the inflammatory response compared to the inflammation produced when only croton oil was used.[17]

4.2 Antimicrobial activity

V. amygdalina extract showed different antimicrobial activities according to the type of extract and target bacteria, where the hot aqueous extract was most effective against *Pseudomonas aeruginosa* with a zone of inhibition of 13.00 mm at 200 mg/ml compared to only 6.00 mm against *Staphylococcus aureus*, while the cold aqueous extract only affected *P. aeruginosa* (10.50 mm); the hot ethanol extract was active at doses of 50 and 125 mg/ml and was more effective against *Streptococcus mutans* than the aqueous extract with a zone of inhibition increasing from 2.00 mm (25 mg/ml) to 10.00 mm (200 mg/ml), while *S. aureus* remained low sensitive to the ethanol extract of *V. amygdalina*. [17]

4.3 Antimalarial activity

V. amygdalina is traditionally used to treat malaria in southern Nigeria. Its ethanol extract is effective against *Plasmodium berghei* depending on the dose, while its aqueous extract is also active against *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.[17]

4.4 Antifungal activity

Sesquiterpene lactones are known to have potent antifungal properties, and the presence of vernodalol and vernolide, which are two components of this group in *V. amygdalina* leaf extract, enhances its antifungal activity, particularly against *Penicillium notatum* and *Aspergillus flavus*, with LC_{50} values of 0.4 mg/ml, respectively.[19]

4.5 Anticancer activity

Breast cancer is the second leading cause of death in women, according to the American Cancer Society (2016). *V. amygdalina* leaf extract can diminish the growth of MCF-7 and MDA-MB-231 cancer cells, but G1/S cell cycle termination only occurs in MCF-7. It is estimated that around 70% of breast cancer cases express ER-α. In addition, the epivernodalol component found in the methanol extract of *V. amygdalina* leaves was found to be active against HT-144 skin melanoma cells. In contrast, administration of the aqueous extract to rats for four weeks at a dose of 10–100 μg/ml per day caused a significant decrease in CYP1A2 expression. Moreover, methanol and chloroform extracts also showed inhibitory effects on THP-1 human leukemia monocyte cells with IC_{50} values of 19.1 μg/ml and 243.4 μg/ml respectively. [19]

4.6 Antidiabetic activity

In a study which set out to investigate the antidiabetic effects of the *V. amygdalina*, Enyi & Ajah (2025) found that potential in managing both type 1 and type 2 diabetes mellitus. The extract showed a significant reduction of blood glucose level in mice induced with streptozotocin. Additionally, the isolated phytochemical compounds from the stem and bark of *V. amygdalina*, such as 6β,10β, 14β-trimethylheptadecan-15α-oyl-15-O-β-Dglucopyranosyl-1,5β-olide, shown that they lower the blood glucose level in rats with streptozotocin induced hyperglycaemia. Along the same lines, hot water extracts of *V. amygdalina* revealed to inhibit α-glucosidase activity and magnify insulin secretion by stimulating β-cell activity. The combination of *V. amygdalina* extract and metformin demonstrated synergistic antidiabetic effects, which result in improved glucose control in mice with alloxan-induced hyperglycaemia. Furthermore, the blood glucose level was found to be reduced when using a decoction of African basil and *V. amygdalina*.[20]

4.7 Antioxidant activity

In 2019, Afiqah Syahirah published a paper in which they stated that the ethanol extract of *V. amygdalina* showed to have antioxidant activity from DPPH radical scavenging test. The ethanol extract of *V. amygdalina* demonstrated the highest reducing capacity and DPPH radical scavenging activity effect, when compared to vernodalol and vernolide at 250 μg/mL. When

compared DPPH radical scavenging activity with different extracts at a concentration of 1 µg/ml from roots of *V. amygdalina*, and ethanol extract demonstrated inhibition of 77% of scavenging activity, while the hot and cold-water extracts inhibited 63% and 49%, respectively. All the extracts exhibit inhibition of bleaching of β-carotene, oxidation of linoleic acid and lipid peroxidation induced by Fe^{2+}/ascorbate in a rat liver microsomal. Nonetheless, the methanol extract showed the highest antioxidant activity compared to water and acetone extract, which could be due to the fact that methanol extract is capable of protecting membrane stability in the hemagglutination test.[21]

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4.9 Neuroprotective activity

According to Atolani et al. (2024), Alzheimer's and Parkinson's diseases are neurodegenerative diseases that are major public health concerns globally. This disease is associated with neuronal death and has a profound impact on movement, speech, intelligence, sleep, memory and appetite. In various studies, the neuroprotective role of *V. amygdalina* has been reported, where it improves learning and memory in mice through the modulation of cholinergic neurotransmission, when using aqueous leaf extract of this plant. The leaves have also been shown to protect the brain of the rat from neurodegeneration by regulating the activities of Na^+/K^+ ATPase, ecto-5'-nucleotidase, monoamine oxidase (MAO), acetylcholinesterase, butyrylcholinesterase, and oxidative stress. On the other hand, the methanolic leaf extract has been demonstrated to provide protection against radiation by improving the antioxidant status and brain tissue morphology in mice exposed to gamma rays. Leaf infusions have also shown the ability to stimulate glucose uptake and utilization in the isolated brain. The neuroprotective potential of the alkaloid-rich leaf extract has been demonstrated in a transgenic fruit fly (Drosophila melanogaster) model as well as in rats with scopolamine-induced amnesia.[22]

4.10 Hepato- and Nephroprotective activities

Aqueous and ethanolic extracts of *V. amygdalina* leaves have been reported to protect the liver from hepatotoxicity induced by tetrachloromethane, alcohol, aflatoxin, and others in rat models. The extract also has the potential to reverse hepatic damage. Dietary supplementation with *V. amygdalina* leaves did not show acute hepatotoxic effects. Nonetheless, there are reports that the extract can induce hyponatremia. Further studies have found that when other plant extracts are given with *V. amygdalina*, hyponatremia can be reversed but diabetic hypophosphatemia is worsened. In an aspirin-induced gastric ulcer model, the leaf extract also shows gastroprotective effects and prevents renal damage. [22]

4.11 Analgesic activities

Atolani (2024) investigated the antinociceptive effects of *V. amygdalina* extract using acetic acid-induced writhing models, formalin test, and tail-flick test. Based on the results, the extract successfully inhibited the writhing response induced by acetic acid and formalin. [22]

4.12 Antipyretic activities

The aqueous extract of *V. amygdalina* leaves along with the saponin fraction showed antipyretic activity, with acetylsalicylic acid used as the standard. The results of the study found that both the extract and the saponin fraction significantly ($p<0.05$) reduced rectal temperature at doses of 100 and 200 mg/kg. The antipyretic activity was reported to be higher in the leaf extract than in the root extract.[17]

4.13 Anti-obesity activities

The anti-obesity activity of *V. amygdalina* was studied in rats induced with a high-fat diet. Rats were given the aqueous extract at doses of 100 mg/kg bw and 500 mg/kg bw. The results of the study showed a decrease in the weight of the rats related to the phytochemical content of this plant, in addition to a decrease in insulin and leptin levels in the treatment group. The anti-obesity effect of *V. amygdalina* in obese rats induced with a cafeteria diet was also evaluated. The extract was given at a rate of 5% and 15% with the diet, while the control group received Orlistat (5.14 mg/kg). The results showed a decrease in weight gain of 12.78% and 38.51% in the treatment group, with a reduction in body fat of 28.04% and 30.02% at doses of 5% and 15%, respectively. Intake of 15% extract also decreased serum triacylglycerol, serum cholesterol, and brain cholesterol levels.[18]

4.14 Improvement of digestion

V. amygdalina contains quercetin, a drug that has been shown to be effective in reducing inflammatory bowel disease (IBD). Quercetin, a natural anti-inflammatory agent, can reduce inflammation in the intestines, thereby improving gut health and reducing stomach discomfort. In addition, bitter leaves are also rich in fiber, which is important for healthy bowel function. A diet high in fiber helps prevent constipation and other digestive problems.[23]

4.15 Cathartic effect

The cathartic effects of *V. amygdalina* were studied using charcoal administered to rats. Doses of 50, 100 and 200 mg/kg of extract were administered to separate groups. The results showed an increase in charcoal motility and stool volume, emphasizing the laxative activity of this plant. [18]

4.16 Anxiolytic and sedative activities

Kaur (2019) investigated the anxiolytic and sedative effect on *V. amygdalina* leaves. The aqueous extract of *V. amygdalina* leaves was found to have anxiolytic activity. At a dose of 50 mg/kg, the extract significantly increased the frequency of head dipping in the holeboard test. In the T-maze apparatus, the latency to exit the closed arm was significantly reduced, while the latency to leave the open arm was significantly increased. These results confirmed the anxiolytic effect of the *V. amygdalina* extract. At doses of 100 mg/kg and 200 mg/kg, the *V. amygdalina* extract significantly reduced rearing and locomotion in the open field test, decreased the frequency of head dipping in the holeboard, and improved inhibitory avoidance and performance in the one-way escape task in the elevated T-maze. In addition, the extract dose-dependently prolonged the duration of amylobarbitone-induced sleep and reduced sleep latency, indicating a sedative effect at higher doses.[17]

4.17 Antimutagenic activity

Detailed examination of prior studies by Kaur (2019) showed that the petroleum ether extract showed the highest activity, followed by the methanol extract and the ethyl acetate fraction. All three *V. amygdalina* extracts were evaluated for their antimutagenic activity on ethyl methane sulfonate-induced mutations in *Salmonella typhimurium* TA100. The results showed that the extracts were able to inhibit His-to-His+ mutations by more than 60%. Among the extracts tested, the petroleum extract had the highest antimutagenic ability, while the methanol and ethyl acetate extracts showed the lowest activity. [17]

4.18 Haemolytic activity

The hemolytic activity of *V. amygdalina* was studied in vitro and the results showed significant hemolysis of erythrocytes ($p<0.05$). Genotypes SS (1024) and AS (512) were identified as the most susceptible to hemolysis induced by *V. amygdalina*, while genotype AA (256) was found to be resistant to the effect. However, *V. amygdalina* extract did not significantly affect other hematological parameters such as red blood cell count (RBC), hemoglobin concentration (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). In addition, no significant changes were observed in platelets, neutrophils, total white blood cell count (TWBC), lymphocytes, eosinophils, and monocytes. [17]

4.19 Antifertility activity

The ethanolic extract of *V. amygdalina* leaves showed antifertility effects of up to 95% in isolated rat uterus. This effect was observed at doses of 0.385, 0.5, and 1.0 g/kg body weight, compared to acetylcholine (1 g/kg) as the control agonist. The results showed a significant decrease in the average number of implantation sites, the number of live fetuses, and the survival rate.[19]

4.20 Anti-leukaemia activity

Root cultures using cold water, hot water, and ethanolic extracts of *V. amygdalina* were tested on patients with acute leukemia and myeloid leukemia. The results showed that the extract provided higher levels of anti-leukemia activity in patients. [19]

4.21 Antidiarrheal activity

Through a review of existing studies, Ugbogu (2021) reported that *V. amygdalina* extract exhibited antidiarrhoeal activity against castor oil–induced diarrhoea in rats, with the extract obtained via cold maceration using 80% methanol. Only at the highest dose (400 mg/kg bw) did the extract show a significant reduction in diarrhoea onset, stool frequency, and stool weight, underscoring its antidiarrhoeal potential. On the other hand, it was also found that *V. amygdalina* extract was effective against *Vibrio cholerae*–induced diarrhoea. The experimental rats were injected with 100 μL of the bacteria, and treatment with 250 mg/kg of the extract showed anti-inflammatory and anti-secretory activity in tissues, further confirming the antidiarrhoeal properties of this extract. [18]

5. HERBAL FORMULATION AVAILABLE FOR *VERNONIA AMYGDALINA*

5.1 Effervescent Granules

A study by Sari et al. (2022) investigated the formulation of the extract of *V. amygdalina* into effervescent granule dosage form in order to improve its use and therapeutic application. The leaves of *V. amygdalina* were macerated in 96% ethanol and the extract was evaporated to obtain a concentrated extract for this study. The effervescent granules were then prepared by wet granulation method with 10% of the extract. This formulation method was developed to overcome the problems of poor patient acceptance, poor dispersion and ease of administration when compared to the conventional crude formulations. The granules formulated were then tested for physicochemical properties such as Hausner ratio, porosity, particle size distribution, moisture content, angle of repose, dispersion time and pH. The outcome showed that the formulation fulfilled the acceptable criteria for most parameters, which indicated satisfactory quality and stability of the granules. But there were some restrictions on compressibility and flowability, which indicated further optimization. Furthermore, the study revealed that there was no significant reduction in the content of flavonoids in the formulated sample when compared to the crude extract, which was attributed to the key bioactive properties. Therefore, it was concluded from this research that pharmaceutical formulation strategies have been proven to be feasible with pursuance of the enhancement of the delivery and functionality of *V. amygdalina*, however, it is required to optimize the formulation parameters for an enhanced performance.[24]

5.2 Effervescent Powder

The formulation-based study has recently shed light on the formulation of *V. amygdalina* into new dosage forms to maximize its therapeutic use. The formulation of effervescent powder of ethanol extract of *V. amygdalina* for enhancing α-Amylase inhibitory activity to enhance its potential as an antidiabetic agent was developed by Isna Zulfiyana (2024). The dried leaves were extracted in ethanol by maceration and the extract was concentrated in this study. This extract was then prepared as an effervescent powder with the addition of sodium bicarbonate, organic acids being citric acid and tartaric acid, which helped it dissolve rapidly with the release of carbon dioxide. Other excipients such as lactose, sucrose and sodium carboxymethyl cellulose (CMC-Na) were added to give an improvement in palatability, stability and to neutralize the inherent bitter flavor of the plant. The optimum composition of the formulations was found by preparing multiple formulations with different concentrations of extract and sweetening agents. The organoleptic properties, moisture, pH and dispersion time were key parameters used to evaluate the developed formulations. Stability after short-term storage was better in a tested formulation which had minimal changes in physical appearance, near neutral pH, low moisture content and dispersion was attained within about two minutes. The results obtained show that the effervescent powder formulation possessed the acceptable quality parameters for use in practical level. Moreover, the study highlighted the potential of formulations to assist in the delivery of bioactive compounds from plants for anti-diabetic purposes, but further biological evaluations were suggested to prove the efficacy of these formulations.[25]

5.3 Microcapsules

The formulation-oriented approach has been reported by Setiani et al. (2026) who developed the microcapsules with plant extracts from *V. amygdalina* as a potential antihypertensive therapeutic candidate. For this study, the plant extract was encapsulated in a microencapsulation system for the purpose of increasing its stability and availability of bioactive components,

as well as to improve its controlled release properties. The formulation process consisted in encapsulating the extract in appropriate polymeric materials to address the drawbacks of plant extracts such as degradation, low bioavailability and variable therapeutic response. The strategy mirrors the increasing use of microencapsulation technology in the delivery of herbal drugs to realize the desired therapeutic benefits of plant-based products. The formulated microcapsules were then characterized in terms of their physicochemical properties and suitability as a delivery system. Different parameters were evaluated including particle size, encapsulation efficiency and structural parameters to decide the quality and performance of the formulation. The findings revealed that microcapsules were effective in trapping bioactive compounds in *V. amygdalina* with increased stability and sustained release. The study has shown the significance of this formulation for antihypertensive properties; thus, microencapsulation might be used to extend the application of herbal extracts in medicine. It is therefore clear from the study that there is a need for novel formulations of natural drugs.[26]

5.4 Ointment

Other formulation strategies have been investigated for improving the therapeutic application of *V. amygdalina*, such as topical delivery for fungal diseases. In the study on antifungal activity of an ointment formulation of *V. amygdalina* leaf extract, Olusolaisaac & Nbangnyong (2017) prepared the extract from the leaves of *V. amygdalina*. In the present study, the leaves were extracted using an appropriate solvent system to get the crude extract which was later added to the ointment base. To find the best formulation, different ointment formulations were prepared by changing the concentration of the extract. The topical dosage form was designed to allow for targeted delivery of the drug, aid in the maintenance of the drug at the site of infection, and promote compliance from the patient relative to traditional crude formulations. Evaluation of the formulated ointments were carried out for physicochemical parameters like homogeneity, spreadability and stability followed by antifungal screening with selected fungal strains. The results showed satisfactory physical properties of the formulations suitable for topical application. Interestingly, the antifungal activity was concentration-dependent, that is, higher concentrations of the extracts were more effective in inhibiting the fungal organisms. The results reveal that the use of the ointment base containing *V. amygdalina* can be used as an effective topical antifungal therapeutic agent with better applicability. Therefore, the findings of the study emphasize the promise of formulation-based methods for delivering and optimizing plant-based ingredients for skin care.

5.5 Liquid Hand Soap

In a study that developed a liquid hand soap with leaf extract of *V. amygdalina*, an alternative formulation approach that uses hygienic applications was investigated, as well as its antibacterial effect.[27] The leaves were extracted with ethanol by maceration process for the extraction of crude extract and were used in the formulation of hand soap in this study. The formulation was designed to harness the antimicrobial properties of plant chemicals such as flavonoids, saponins, tannins, and alkaloids in an easily accessible, everyday product. The inclusion of the extract within the formula of a liquid soap is therefore aimed at emphasizing the practical application within the field of pharmaceutical and cosmetics to improve its usability, availability, and effectiveness in combating any bacteria. The hand soap formulation prepared in the laboratory was then subjected to a test to determine its effectiveness in inhibiting the growth of *Escherichia coli*, which is a pathogenic microorganism associated with hygienic-related infections. It was observed that there was indeed some level of inhibition. The implications of this are that the biological activity of plant extracts may be maintained when used in topical cleansing products, yet provide a useful health benefit. Thus, the study emphasizes the potential of formulation-based approaches in transforming crude plant extracts into functional products with enhanced applicability in infection control and public health.

5.6 Hair Shampoo

A research work aimed at exploiting the therapeutic potential of plant extracts into actual personal care products, created a natural hair shampoo containing the leaf extract of *V. amygdalina* as an herbal active ingredient.[28] The leaves were extracted with different solvents and phytochemical screening of essential bioactive components was performed in this research. The antioxidant and antimicrobial activities of the extracts were also assessed to identify the best extract for formulation. The ethanolic extract showed the most activity and was hence selected for the formulation of the shampoo. The formulation process included the blending of the extract with the appropriate excipients to obtain a stable and easily used cosmetic product, indicating the possibility of incorporating medicinal plant extracts into the routine hygiene product formulations. The physicochemical properties such as pH, viscosity, foaming and stability of the developed shampoo formulations were then

analyzed and sensory evaluation was conducted to check the acceptability of the user. The results showed that the formulated product had good physicochemical properties and consumer acceptance. Further, the antioxidant and antimicrobial properties of the extract of *V. amygdalina* contributed to significant activities, which aid in the role of this plant in health and hygiene of the scalp. The results of these studies show that plant extracts can be used in cosmetic formulations without destroying their biological activity and can be improved in terms of their applicability to products used in everyday life.

5.7 Tablet

Optimisation studies have also been done for solid dosage forms to optimize delivery of plant-based compounds. Wahlanto et al. (2024) has researched the formulation of tablets containing *V. amygdalina* leaf extract particularly the optimization of the concentration of gelatin as a binder in the formulation. The extract was added to the tablet formulations with different concentrations of gelatin (4%, 5% and 6%) to study the effect of the extract on the physical properties and tablet quality of the tablets. The reason for such a procedure was to produce a convenient oral dosage form with uniformity and stability of the active constituents and increased patient compliance. The formulated tablets were subjected to various standard physicochemical tests such as angle of repose, compressibility, weight uniformity, thickness, hardness, friability and disintegration time. All the formulations were found suitable for oral administration as the results showed that all the formulations were within the limit of acceptability regarding flow properties, weight uniformity and disintegration time. The mechanical properties of the tablets were affected by the change in concentration of gelatin, however, only the tablets prepared with higher concentration of binder met the friability requirement. The study findings indicate that optimization of the tablet formulation necessitates the optimization of the binder to ensure that the tablets exhibit the desired properties, and that this optimization of the formulation can contribute to the improvement of the quality and efficacy of pharmaceutical products.[29]

5.8 Suppository

A formulation driven investigation was carried out to investigate the therapeutic potential of *V. amygdalina* against vulvovaginal candidosis as suppositories dosage form.[30] The aqueous leaf extract of *V. amygdalina* was formulated into suppository using appropriate base materials in this study to achieve good localized delivery in the vaginal environment. The optimization of the formulation was carried out by adjusting the composition of the suppository base to obtain a suitable melt, drug release and stability. The various formulations were made and subjected to in vitro characterization to study their physicochemical properties and suitability for further development towards clinical application. Key parameters like weight uniformity, melting time, hardness and drug release profile were investigated in the formulated suppositories. Furthermore, antifungal activities were carried out against *Candida albicans*, which causes most cases of vulvovaginal candidosis. It was discovered that the suppository preparations possessed physicochemical properties capable of releasing the extracts in a controlled manner. In addition, it was established that the preparations were highly effective against *Candida albicans*, hence can be used in the treatment of vulvovaginal candidosis. Generally, from the study conducted by these researchers, it is evident that *V. amygdalina* suppositories appear to offer a promising remedy, although further investigation is required to test their efficacy and safety in humans.

5.9 Silver Nanoparticles

The use of formulation strategies based on nanotechnology is a newer technique that has been explored to increase the therapeutic potential of plant-based compounds. A.C. Ovenseri (2023) isolated silver nanoparticles (AgNPs) using the leaf extract of *V. amygdalina* using a green synthesis approach to enhance its antioxidant and antibacterial activity. In this study, the natural plant extract was used to synthesize the nanoparticles without the aid of any synthetic chemical substances for reduction and stabilization of the particles. Different analysis methods were employed in the characterization of the synthesized nanoparticles using different equipment such as scanning electron microscope and x-ray diffraction. From the results obtained, it was found that the nanoparticles had spherical shapes, polydispersed in size ranges between 70-90 nm, and x-ray diffraction showed crystalline structure. The biological activities of formulated nanoparticles were also tested and compared with the crude extract. Antioxidant activity was determined using the DPPH radical scavenging method, and it was observed that the synthesized silver nanoparticles had higher antioxidant activity (IC_{50}) when compared to the crude extract. In addition to that, the antibacterial activity was evaluated using the disk diffusion test for two different bacteria namely *Escherichia coli* and *Staphylococcus aureus*, where it was found that the synthesized nanoparticles have excellent antibacterial activity. The bioactivity of the *V. amygdalina* was not only retained in the nanoformulation, but it was even enhanced.[31]

5.10 Electrosprayed Particles

V. amygdalina leaf extract antifungal activity was improved by using formulation-based strategy with advanced particle engineering technology against plant pathogens. The research by Tipduangta et al. (2023) involved the fractionation of leaves of *V. amygdalina*, which was used to obtain the most active fraction against fungi and then encapsulated in polymeric micro/nanoparticles with electrospray technique. Fractions selected, especially high in alkaloids, exhibited significant inhibitory effect on *Phytophthora nicotianae*, one of the most important causative agents of citrus root rot. This active fraction was then sprayed using the electrospray technique and polymer matrices like polyvinyl alcohol (PVA), and cellulose acetate (CA), with optimization of the polymer matrix composition and the loading of the active fraction to ensure the stable formation of particles. The particles formed were mainly in the micro- to nanoscale between 0.75-0.98 μm. Morphology, particle size and compatibility of the formulated electrosprayed particles were determined using methods such as scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). The antifungal activity was also assessed by the inhibitory activity of *Phytophthora nicotianae* in vitro. The results showed that the extract loaded particles were effective in inhibiting fungal growth and that the particle that contained both PVA and CA exhibited better inhibition results as the release of the active compounds was better. Conversely, the formulations containing cellulose acetate only had slower release and less antifungal effects. The study overall showed significant improvement in the formulation of *V. amygdalina* extract using electrospray technique and its antifungal efficacy, thus suggesting its potential as a sustainable plant-based alternative to control plant diseases like citrus root rot.[32]

5.11 Novel Herbospheres

A new formulation technique was investigated, namely particulate-based formulation using the leaf extract of *V. amygdalina* by Sa et al. (2018). The leaf extract of *V. amygdalina* was formulated into a herbosphere delivery system which was aimed at improving the stability of the herbal constituents and better controlled release of them. Formulation of plant spherical particles (herbospheres) was prepared with the help of suitable polymers to facilitate the entrapment of the plant extract. The major drawback of the conventional herbal preparations is their rapid degradation and poor bioavailability of active phytoconstituents, which are addressed with this delivery system. The formulated herbospheres were tested for the important physicochemical properties such as particle size, flow characteristics, entrapment efficiency, and in vitro drug release profile. The results showed that the prepared herbospheres had a good spherical shape with an acceptable encapsulation efficiency, which showed the successful incorporation of plant extract into the polymer matrix. Furthermore, the release profile of the formulation showed a slow and sustained release pattern which was more favorable than crude extract administration. In general, the study concluded that the stability and performance of the leaf extract of *V. amygdalina* could be improved using herbosphere-based delivery systems, which can be used in future to develop advanced herbal drug delivery systems.

5.12 Spray Gel

A variety of topically applied delivery systems has been researched to enhance the therapeutic efficacy of medicinal plant extracts in wound management applications. Novitasari et al. (2025) formulated a sprayable gel film-forming formulation with *V. amygdalin*a leaf extract, and assessed its ability to be used as a formulation for diabetic wound healing. The research in this paper involved using the leaf extract in a polymer-based gel system which could be applied to the skin surface and form a thin protective skin layer. The formulation was developed to increase the coverage of the wounds, to extend the time of drug activity in the wounds and to ensure a controlled release of bioactive compounds. The focus is on how modern pharmaceutical technology is combined with traditional medicinal plants to treat complex issues like diabetic wounds. The physicochemical properties suitable for topical application, such as pH, viscosity, spray pattern, film forming ability and drying time of the formulated spray gel film were evaluated. Further, in vitro wound healing related studies were conducted to check the therapeutic potentiality. The results showed the formulation gave rise to a uniform, stable and flexible film with acceptable application characteristics. Moreover, the effect of *V. amygdalina* extract resulted in improved wound healing ability, owing to its antimicrobial properties and active ingredients which aid in tissue repair. As such, the study showed that spray-gel film forming systems have a great potential for the delivery and efficacy of *V. amygdalina* in diabetic wound care.[33]

5.13 Nanoemulsion

An approach to sustainable plant disease management based on the formulation of emulsion-based products containing the leaf extract of *V. amygdalina* was explored. Yusoff et al. (2021) developed a delivery system for nanoemulsion with

dichloromethane extract of *V. amygdalina* as active antifungal agents against gray mold disease in tomato plants caused by *Botrytis cinerea*. The optimization of oil-surfactant-water ratio in the formulation process led to multiple emulsion systems (F1-F8), obtained using the ternary phase diagrams. They had developed these formulations using environment friendly surfactants and oil carriers for improving solubility, stability and delivery of the bioactive compounds. Eight formulations were then developed and studied in detail for their physicochemical characteristics to assess their potential for use as botanical fungicides. The developed nanoemulsions were tested for their stability, particle size distribution, zeta potential, polydispersity index, viscosity and surface tension. Physicochemical properties of these formulations such as low viscosity, stability and small particle size (around 66-140nm) for both F5 and F7 formulations were found to be better. Furthermore, the antifungal activity was evaluated in vivo against fruits of tomato plants infected with *Botrytis cinerea* and treated with the product. The results showed that the F5 formulation had a most significant antifungal effect, whereas F7 had a marked effect on reducing the disease occurrence, both in terms of incidence and severity. The results suggest that the emulsion-based formulation has a substantial impact on the stability and antifungal activity of *V. amygdalina* extract, demonstrating its potential for sustainable use in agriculture as an alternative to chemical fungicides.

6. FORMULATION AVAILABLE FOR *V. AMYGDALINA* AS COMBINATION THERAPY

6.1 Cream incorporating *V. amygdalina* and *Calotropis procera* leaf extracts

Combination based formulation of medicinal plants has been studied, aiming at taking advantage of the synergic therapeutic properties of various medicinal plants in the treatment of skin infections. Kola-Mustapha et al. (2017) formulated the cream containing the extracts of leaves of *V. amygdalina* and *Calotropis procera* in order to increase the antimicrobial activity for dermatological use. Both plant extracts were extracted and added to a cream base to different concentrations to find out the optimum formulation for the most effective results. The rationale for the combination of these extracts was that bioactive constituents in the extract are complementary so that therapeutic effects would be better than using individual plant extracts. The cream base was carefully selected to ensure the dispersion of extracts, their stability and suitability for topical application. The physicochemical properties (pH, viscosity, spreadability and stability) and antimicrobial activity of the formulated creams against selected pathogenic microorganisms associated with skin infections were evaluated. It was found that the combination formulations had acceptable physical properties that are suitable for topical use. Most significantly, the antimicrobial effects of the creams produced with both *V. amygdalina* extract and *Calotropis procera* extract was amplified when compared to those of the single extracts, indicating possible synergistic effects. The findings of this study have shown a possibility to improve the therapeutic activity of plant products by combining herbal products and to facilitate their application in the control of skin infections.[34]

6.2 Capsules containing *V. amygdalina* and *Gongronema latifolium* extracts

In recent years, formulations containing more than one herb have been studied to improve their therapeutic effects by the combination of bioactive compounds found in the plants. *V. amygdalina* and *Gongronema latifolium* extracts were combined to make capsules which were tested for their antidiabetic effects in a study by Adikwu (2022). The plant materials were extracted with suitable solvents and then formulated in capsule dosage form to produce an accurate capsule dosage and enhance patients' compliance. The combination approach was designed to take advantage of the complementary pharmacological characteristics of the two plants, especially in the treatment of diabetes mellitus. The formulated capsules were developed as the oral delivery system to achieve systemic delivery of bioactive constituents. The formulation was evaluated in vivo in a streptozotocin-induced diabetic rat model for its therapeutic efficacy. To assess the antidiabetic effect of the formulation, certain parameters like blood glucose, body weight, biochemical markers etc. were monitored. The outcomes revealed that the polyherbal capsule formulation was found to be effective in lowering blood glucose level and improving blood metabolic parameters, when compared to diabetic control groups. Moreover, *V. amygdalina* and *Gongronema latifolium* showed significant anti-diabetic effect, indicating that both extracts have a synergistic effect. The results herein reinforce the potential for combination herbal formulations to enhance clinical outcomes for diabetes and their relevance in developing novel therapeutic strategies.[35]

6.3 Lozenges containing freeze dried aqueous extract of *V. amygdalina* and Glibenclamide or Metformin

For the purpose of improving the therapeutic efficacy in the management of diabetes, an integrated approach of the formulation of herbal extracts along with antidiabetic drugs has been studied. Dorathy et al. (2024) has formulated the lozenges of freeze-dried aqueous extract of *V. amygdalina* with glibenclamide as well as with metformin and intended to achieve the dual-action

effect for glycaemic control. For this research, the aqueous extract of *V. amygdalina* was freeze dried to preserve its bioactive components and subsequently added to lozenge dosage forms along with standard antidiabetic agents. The formulation was developed to offer an easy-to-absorb, oral delivery system which may also offer an improved method of patient adherence and make the most of the herbal and synthetic therapeutic effects. The lozenges were evaluated for the physicochemical properties to ensure it meets the requirements of a solid dosage form including hardness, friability, weight uniformity, and dissolution. Furthermore, the antidiabetic activity of the formulations was evaluated in vivo by measuring blood glucose level. The results showed that the combination formulations significantly lowered blood glucose as compared to the individual treatments, suggesting possible synergism of the interaction between the extract of *V. amygdalina* and the conventional drugs. The results of this study indicate that the use of herbal extracts in combination with conventional pharmacotherapy could be a promising approach for diabetes management without compromising formulation properties.[36]

6.4 Biscuits incorporating leaf powder of *V. amygdalina* in combination with *Heteroclarias* spp. Viscera Oil

Another way of delivering the therapeutic and nutritional properties of medicinal plants has been tried through functional food-based formulations. Soji-Omoniwa et al. (2024) formulated fortified biscuits with the addition of the powdered leaf of *V. amygdalina* and the viscera oil of *Heteroclarias* spp., to improve the nutritional and functional attributes. The proportion of *V. amygdalina* leaves and fish viscera oil varied in the biscuit formulations in this research to produce food products with high nutritional value. The purpose of these additions was to enhance the protein, lipid and micronutrient contents, as well as the addition of bioactive compounds from the medicinal plant. This way, people are more interested in incorporating medicinal plants into their daily diet products to ensure health and disease prevention. The formulated biscuits were analyzed for their proximate composition including protein, fat, moisture, ash content as well as their sensory attributes namely taste, texture, aroma and overall acceptability. The results showed that the biscuits produced with *V. amygdalina* and fish oil significantly improved their nutritional content, especially when it comes to essential fatty acids and proteins. In sensory evaluation certain formulations were found to be acceptable in terms of consumer preference, although the higher concentrations of *V. amygdalina* slightly affected the taste because of its bitterness. Therefore, as revealed in the study, the use of medicinal plant materials in functional food products is feasible and can be used as alternatives to the diet for nutritional enrichment and promoting the health of consumers.[37]

6.5 Beverage incorporating Bitter Leaf (*V. amygdalina Delile*) extract with Lemon (*Citrus limon*) and Honey

There is a need for a functional beverage formulation approach that will increase palatability as well as make health benefits from the utilization of the extracts from plants. Cornelia et al. (2025) came up with a beverage formulation involving *V. amygdalina* extract in conjunction with lemon (*Citrus limon*) and honey with the objective of making a product with better sensory acceptability and with some antioxidant properties. Bitter leaf extract was made by macerating the plant in three types of solvents (ethanol, ethyl acetate, and hexane) for different periods, where an extract made by maceration in ethanol for two days was chosen for formulation due to its exceptional properties. This extract was mixed with varying amounts of lemon and honey in varied ratios. The resultant beverages were assessed for their antioxidant activities, physiochemical parameters like pH, colour, total titratable acidity and total soluble solids, and sensory evaluation based on hedonic scale. It emerged that a formulation of 10 ml of bitter leaf extract with a lemon to honey ratio of 1:1 had the best balance between bioactivity and palatability since it had high antioxidant capacity (IC_{50} = 7.91%) with appreciable amount of phenolic and flavonoid components. Furthermore, the use of honey and lemon significantly reduced the extract's natural bitterness without compromising its therapeutic characteristics. In order to increase consumer acceptability and therapeutic value, the research emphasizes the potential of incorporating *V. amygdalina* with various other natural constituents in functional beverage compositions.[38]

7. DISCUSSION

This present review aims to focus on the wide pharmaceutical and biotechnological potential of *V. amygdalina* as it relates to its use in various formulation systems and combination therapies. In general, the results from the previous studies have shown that *V. amygdalina* is a highly versatile medicinal plant that has been successfully processed in various forms such as tablets, capsules, creams, gels, suppositories, emulsions, nanoparticles and functional foods. All of these formulation strategies share the common goals of mitigating the drawbacks of crude plant extracts such as low stability and poor bioavailability and inconsistent therapeutic activity. This is consistent with past reports, which have already discussed the need for formulation strategies to enhance the clinical applicability of herbal medicines.

Across reviewed studies, formulation science is one of the critical factors that influences *V. amygdalina* delivery and its function. For example, to enhance oral administration and patient acceptability of the drug and simultaneously preserve good physicochemical properties and acceptable dispersion profiles, granules and powders were developed, which are effervescent.[25] Likewise, tablet preparations of optimized binder content properties exhibited good mechanical strength and disintegrating properties, indicating the significance of excipient optimization in solid dosage form.[24] Local delivery systems like topical ointments, creams and spray gel film-forming systems, exhibited promising antimicrobial and wound healing properties, demonstrating that biological activity can be maintained and therapeutic effects enhanced when delivered to a specific site.[28,33] The use of advanced systems like herbospheres, microcapsules, electrosprayed particles and nanoemulsions further showed great controlled release, stability and antifungal activity, demonstrating the increasing trend toward nanotechnology-based herbal drug delivery systems.[26,39,40]

Combination formulations of *V. amygdalina* have also exhibited better therapeutic potential due to synergy. In the study of combined extracts of *V. amygdalina* and *C. procera* in creams, there was an increase in antimicrobial activity compared to the individual extracts, implying a possible synergism in topical treatment of infections.[34] Similarly, oral combination products containing *Gongronema latifolium* and synthetic antidiabetic agents like metformin or glibenclamide showed strong hypoglycaemic activity in diabetic models, suggesting enhanced metabolic control via multi-target activity.[35] These include use in functional food products like biscuit fortified with *V. amygdalina* and fish oil, and in beverages with lemon and honey, which highlight the incorporation of the extract into dietary approaches for health promotion and disease prevention.[37,38] Although such results are encouraging, most of the studies do not fully explain the mechanisms involved in the synergy, and uncertainties exist if the observed effect is additive or truly synergistic.

The therapeutic potential of *V. amygdalina* may be explained by its rich bioactive compound profile, such as sesquiterpene lactones (vernodalin, vernolepin, vernodalol), flavonoids (luteolin, apigenin derivatives), coumarins and phenols.[17,18] These constituents show a broad spectrum of pharmacological properties, such as antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anticancer, antifungal, antiviral, hepatoprotective and neuroprotective properties. The variety of compounds is indicative of the multi-target therapeutic properties of the plant and the content of these compounds could be responsible for the different formulation systems in which the plant is effective. Although these have been encouraging results in a number of formulation systems, the majority of studies are still preclinical in nature with very limited clinical validation and incomplete understanding of mechanisms involved in interactions. The identified gaps suggest the need for additional research that is more standardized and clinically oriented to completely define the therapeutic potential of *V. amygdalina*-based formulations.

However, the studies reviewed largely established the pharmacological potential of *V. amygdalina* using in vitro models and animal experiments, whereas evidence from clinical studies remained scarce. Experimental findings provided support for associations between the plant's phytochemical constituents and its observed biological effects. In most formulation studies, performance was assessed through physicochemical properties, stability, drug-release behaviour, and biological assays, rather than through direct measurement of bioavailability or evaluation of clinical efficacy. In addition, differences in the source and quality of plant material, extraction methods, and formulation composition underscore the need for standardization. Further research is therefore warranted on toxicity, herb–drug interactions, and clinical safety. More rigorous experimental work is also needed to establish whether synergistic effects reported in combination formulations are scientifically demonstrable rather than preliminary or merely inferred.

The overall studies indicate that the *V. amygdalina* has a significant potential for development into a multi-functional medicinal plant, which can be added to the advanced pharmaceutical formulations and functional formulations. Yet, if it is ever to be translated from experimental research to clinical practice, formulation systems need to be optimised, extraction methods standardised and a thorough pharmacological validation needs to be carried out. Nanotechnology delivery systems, combination therapy and functional food applications are potential areas of future research. These developments could contribute to the integration of traditional usage and evidence-based medicine in the production of effective, safe and standardized therapeutic products using *V. amygdalina*.

8. LIMITATION

Some limitations still exist in the current body of literature as whilst numerous studies proved the efficacy of *V. amygdalina* either alone or in combination formulations. Investigation of many of these findings is still limited to in vitro assessments, animal models or laboratory characterization studies and has yet to be translated into clinical trials—making it difficult to validate safety and indeed therapeutic efficacy in humans. Moreover, while combination formulations (e.g., capsules, creams and lozenges) showed significant synergistic effects but most studies are not conducted through full pharmacokinetic and pharmacodynamic profiling thus lacking adequate knowledge in the elucidative interaction mechanisms of *V. amygdalina* with other plant or synthetic agents.

Furthermore, the differences in extraction, formulation, and dosage standardization add to the variability in reproducibility in the studies. Most formulations also do not adequately address long-term stability, drug-drug or herb-herb interactions, and toxicity profile, which are important for clinical translation. Nevertheless, some advanced drug delivery systems have been invented in the past, but many of these are yet to be developed, tested, and validated by the regulators. Hence, there is need for further investigation involving *V. amygdalina* extract formulations using standard formulations and interactions with other drugs to exploit the medicinal value of this drug.

9. RECOMMENDATION

The potential of *V. amygdalina* formulations should be further explored from preclinical to well-designed clinical trials to confirm safety, efficacy, and thus, the appropriate doses of these formulations in humans. Standardization of extraction methods and formulation protocols should also be ensured for the same so that it could be reproducible and the similar therapeutic effect could be obtained every time. Furthermore, longer term toxicity and pharmacokinetic studies and the effects of herb-drug interactions and herb-herb interactions should be strongly recommended. Creating clinically useful, stable and scalable combination formulations will further aid in the translation of *V. amygdalina* into evidence-based functional and pharmaceutical products.

10. CONCLUSION

Rising research about *V. amygdalina* indicates that it has progressed from being a medicinal herb used for traditional purposes by the local community to becoming an effective medication. Nonetheless, other than its pharmacological aspects, there is the issue of formulating this medicinal herb to fully exploit its potential. The use of this plant in various delivery systems, especially when combined with other bioactive agents, heralds a new era of more focused, multifunctional and patient-friendly herbal medicine. Specifically, the research into polyherbal and hybrid combinations indicates a shift towards the development of therapies acting on multiple pathways of a disease, a complementary path. However, some of the transition steps from experimental formulations to clinically relevant products are limited and there is a need for more stringent testing and standardisation. The research on this topic should be continued to further emphasize translation studies, interaction profiling, and scalable formulation design. In conclusion, the future of *V. amygdalina* is not just in its biological activity, but how successfully it can be developed as a safe, reliable and evidence-based therapeutic system.

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AUTHOR CONTRIBUTIONS

Bavithrah Devi Lakshamanan Raja: Methodology, Investigation, Data Curation, Formal Analysis, Writing—Original Draft

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Mahani Mahadi: Data Curation, Supervision, Writing—Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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