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Unveiling the Multi-Targeted Therapeutic Potentials of Vernonia amygdalina: A Comprehensive Review of Bioactive Compounds, Molecular Mechanisms, and Clinical Opportunities

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ABSTRACT:

Vernonia amygdalina (bitter leaf) has been used as traditional medicine across Africa and beyond because of its diverse pharmacological activities. While previous studies have validated its therapeutic potential, a comprehensive understanding of the underlying molecular mechanisms driving these effects remains incomplete. This review critically examines the bioactive compounds present in V. amygdalina, their documented pharmacological effects, and the potential therapeutic applications of this plant, focusing specifically on elucidating the key molecular pathways modulated by its constituents. A systematic literature search was conducted using Web of Science, Scopus, PubMed, and ScienceDirect. Identification and analyses of a wide array of bioactive compounds, including sesquiterpene lactones (vernodalin, vernolepin), flavonoids (luteolin, apigenin), and saponins were carried out. Critical analyses revealed that these compounds exert their effects through multiple, interconnected pathways, including but not limited to the method of extraction, their robust antioxidant and cytoprotective effects, and the direct cytotoxic effects on cancer cells through induction of apoptosis and cell cycle arrest. Bitter leaf is used in the traditional treatment of malaria, diabetes, and gastrointestinaldisorders.Inlightoftheseestablished mechanisms, its antimicrobial properties and its effectiveness in managing metabolic syndromes were discussed. However, significant challenges remain in translating V. amygdalina's therapeutic benefits into standardized and safe clinical applications, including variability in bioactive compound concentrations due to environmental factors and preparation methods, limited data on human bioavailability and pharmacokinetics and a lack of rigorous clinical trials demonstrating efficacy and safety. Addressing these challenges through targeted research into optimized extraction techniques, formulation development, and well-designed clinical studies are crucial. Bitter leaf represents a promising source of novel drug leads, particularly for the development of multi-targeted therapies for complex diseases. Future research should prioritize the identification and validation of specific bioactive compounds responsible for the observed effects and the elucidation of their detailed molecular mechanisms of action.

Keywords: *Vernonia amygdalina, bioactive compounds, therapeutic applications, pharmaceutical potentials, ethnomedicine.*

1. Introduction

Natural products have been critical in drug discovery/development for centuries for several therapeutic purposes [1, 2]. The potential therapeutic benefits of medicinal plant-derived compounds, including enhanced efficacy, minimized toxicity, and increased bioavailability, have revitalized research interest in plants [3, 4]. *Vernonia amygdalina*(bitter leaf) is an angiosperm that belongs to the plant family known as Asteraceae and the genus Vernonia. Of over 1000 species of this genus available, 300 species are common in Africa. Among the four species whose leaves are used as vegetable including, bitter leaf (*Vernonia amygdalina*), sweet bitter leaf (*V. hymenolepis*), star-flowered bitter leaf (*V. colorata*) and country bitter leaf

(*V. thomsoniana*); *Vernonia amygdalina* is most common because of its versatility. It thrives well in tropical Africa and Asia and grows to about 2-5 m high with oval-shaped leaves of about 20 cm [5]. The leaf extracts stems, and barks are of immense significance due to their usefulness for culinary, medical, and curative reasons in many parts of Africa and beyond. In fact, traditionally, it has been effective in the treatment of some common ailments such as fever, stomach aches, malaria, wounds, and so on. [6]. Bitter Leaf's long time track records of medicinal and curative values have earned it recognition in the pharmaceutical space. Notably, the acceptance and usefulness of bitter leaf as an alternative source of medicine is gaining recognition across different countries, including Nigeria [5, 6, 7]. This review is designed to unveil the pharmaceutical worth of *V. amygdalina* and its bioactive compounds, highlighting their potential applications in contemporary medicine.

2. Methodology

A comprehensive literature search was conducted using prominent databases, including Web of Science, Scopus, PubMed, Springer, ScienceDirect, and Google Scholar. English-language publications were exclusively utilized for this review. Relevant studies were identified by employing strategic keyword combinations and concatenation, such as "*Vernonia amygdalina* bioactive compounds," "ethnopharmacology of bitter leaf," and "*Vernonia amygdalina* pharmacology." The search yielded a range of studies examining the phytochemical, ethnobotanical, and pharmacological properties of *Vernonia amygdalina*. The retrieved articles were meticulously reviewed, with particular attention paid to their titles, abstracts, and results.


A


B

Plate 1: Vernonia amygdalina: (A) Life V. amygdalina in a garden located at Ishiagu, Ebonyi State, Nigeria (B) V. amygdalina after its leaf extraction

Chemical composition of bitter leaf

The actual chemical composition, particularly bioactive chemical compounds of bitter leaf, has yet to be fully explored. Notably, substantial scientific evidence exists concerning bitter leaf's increasing usefulness attributable to its vast bioactive compounds (3, 4). The nutritive constituents of the bitter leaf include protein, sugars, iodine, lipids, copper, iron, thiamine, vitamins A and E, etc. [7]. Aside from these nutrient components, it also harbors many secondary metabolites termed bioactive compounds, which are referred to as phytochemicals. These include saponins, coumarins, flavonoids, lignans, alkaloids, xanthones, etc. (Figure 2).

According to a study by Edo *et al.* [7], about 20 different alkaloids of bioactive significance have been detected in bitter leaves. The vast therapeutic applications or effects of the bitter leaf have been attributed to biologically important chemical compounds harbored in its leaf, stem as well as in root. Bioactive members of sesquiterpenes contained in bitter leaf are numerous; they include vernolide, vernolepin, vernodalinol, hydroxyvernolide, vernolic, vernodalin, vernomenin, and vernomydin [7, 8]. Compounds such as Lupeol and α-amyrin are examples of terpenes found in bitter leaves [7, 8, 9]. Studies have also revealed isorhamnetin, rhamnetin, luteolin 7-O-b-gluconide, and luteolin 7-O-b-glucoronoside as important examples of flavonoids in bitter leaves [2, 7, 10]. Ugbogu *et al.* [2] highlighted the vigorous

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antioxidant activities of three flavones, especially luteolin (3´,4´,5,7 tetrahydroxyflavone) present in bitter leaf extract.

According to studies, many bioactive compounds were unraveled in the classes of alkaloids, terpenoids, flavonoids, saponins, and tannins (Figure 2) [2, 7, 11-12]. Based on the studies, the solvents employed for extraction were mainly ethanol and methanol. It is imperative to note that the specific bioactive compounds present in the bitter leaf may vary depending on some factors, which include: the plant's geographic location, growing conditions, processing, and extraction methods.

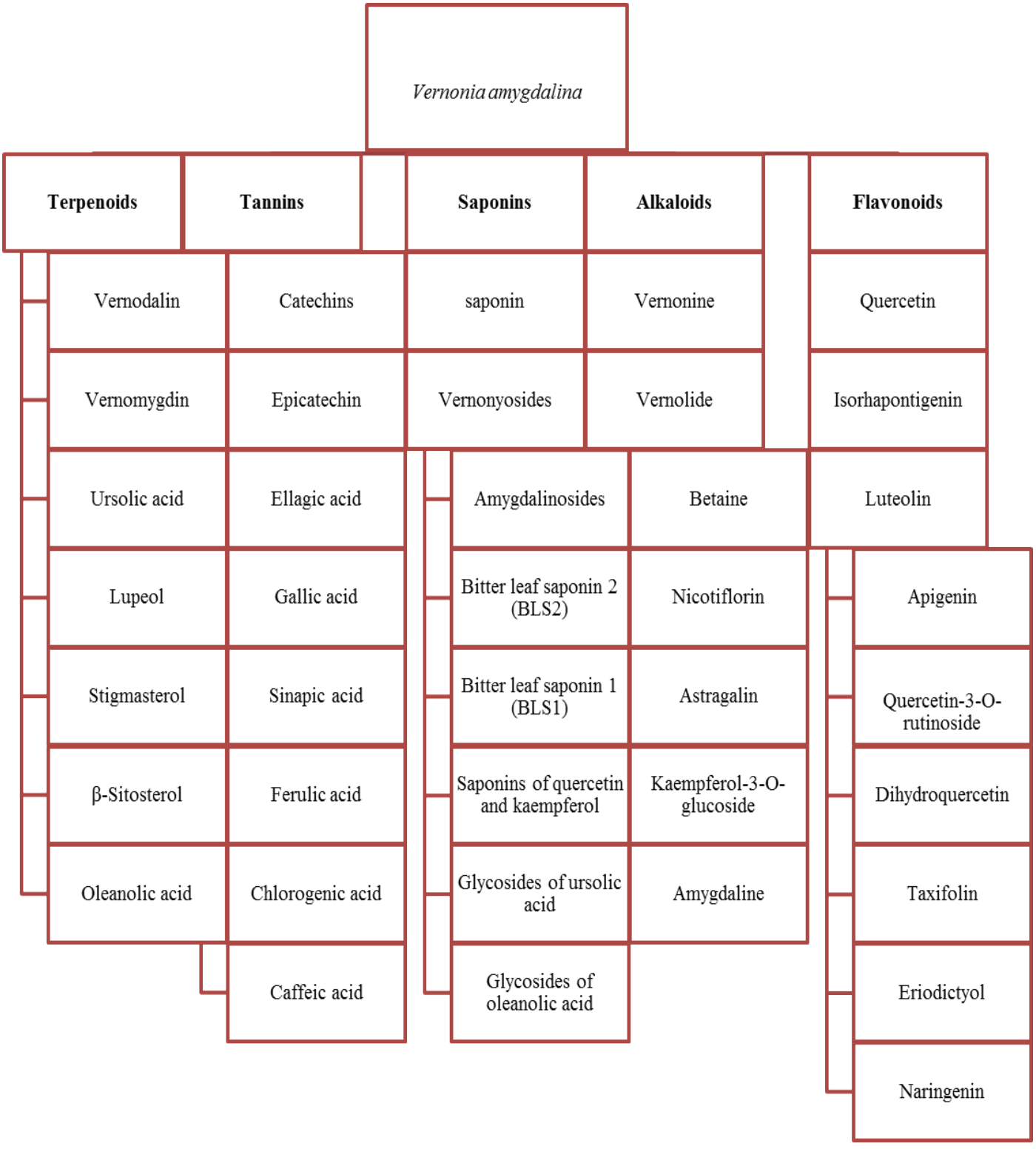

Figure 1: Bioactive chemical composition of bitter leaf

Pharmacological properties of bitter leaf and its bioactive compounds underlying principles of action

Bitter leaf contains interesting bioactive compounds with potential therapeutic applications (Figure 2). Various studies have shown that bitter leaf has significant antimicrobial activity against many bacterial, fungal (yeast inclusive), and viral pathogens: *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Salmonella typhi*. Using chloroform and methanol extraction methods, among others, bitter leaf extracts have been reported to have antimicrobial/antifungal effects against *Staphylococcus aureus, Salmonella enterica, Bacillus subtilis, Klebsiella pneumonia*, *Toxoplasma gondii*, *Pseudomonas aeruginosa, Botrytis cinereal*, *H. contortus*. [2, 7, 9, 13-16]. The alkaloid and flavonoid constituents of the bitter leaf have been reported to be responsible for its antimicrobial activities. Edo *et al*. [7] further reported that bitter leaf generates superoxide radicals, which possess antimicrobial activity by inhibiting the growth and proliferation of human pathogens.

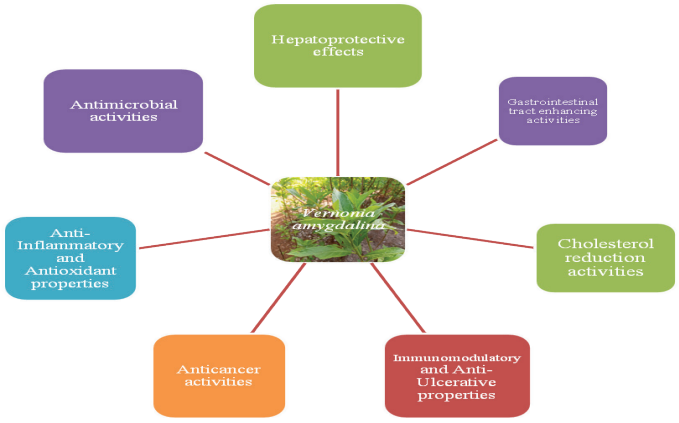

Figure 2: Pharmacological properties of bitter leaf

Many researchers have reported the antioxidant potentials of bitter leaf: in an *in vivo* investigation using mice as a model organism, the extract from the stem-bark of bitter leaf demonstrated free-radical scavenging activities against toxicity caused by acetaminophen, thus depleting the oxidative stress. A significant reduction of brain tissue oxidative stress was also reported on exposure to bitter leaf extracts. Bitter leaf extracts demonstrated antioxidant activity when administrated to a model rat exposed to arsenic-induced free radicals. However, the efficacy of the extract depends on the extraction method used; the leaf extract obtained from the methanol extraction method proved to have the most antioxidant potency when compared with acetone and water extraction methods [2, 12, 17]. It is therefore recommended that the methanol extraction method be utilized for optimal antioxidant benefits of bitter leaf extract.

Several studies have supported the anti-inflammatory potential of bitter leaves. Many bioactive compounds like cynaroside, vernonioside, and zinc oxide isolated from bitter leaf showed anti-inflammatory effects in mice. Bitter leaf extracts exhibited significant anti-inflammatory activities against inflammation, fever, and pain artificially generated in rats using carrageenan when compared to standard drugs (diclofenac) [2, 18, 19]. Bitter leaf contains bioactive compounds like tannins, quercetin, and kaempfero; they have been attributed to its antioxidants' capabilities, which scavenge free radicals, obstruct appropriate pyrogens, and shield vital body components against oxidative stress [9, 7, 20].

Researchers have reported anti-cancerous properties of bitter leaf extracts: their mechanism of action includes the cause apoptosis of infected cells, elevated cell inactivity during the mitotic phase, and obstructed cellular communication networks; the compounds in the extracts assist in suppressing the proliferation of cells. Ugbogu *et al.* [2] reported that the extract of bitter leaf stimulated the production of phosphatidylinositol-3-kinase, which mechanistically triggered the appearance of rapamycin among murine mammary carcinoma cells. Myasita *et al.* [11] further reported the inhibitory activities of bitter leaf extracts against the multiplication of human cancer cells. In the same vein, Yedjou *et al*. [21] reported the potential of bitter leaf extract to obstruct the progression of breast carcinomas. Additionally, bitter leaf extracts have been reported to cause significant depletion in the volume of MDA-MB-468 tumor cells and obstructed MCF-7 and MDA-MB-231 growth [22-23]. The anti-cancer potential of bitter leaf extract is attributed to its sesquiterpene lactones content, notably vernolide and vernodalin, which have been demonstrated to exhibit cytotoxic and ant proliferative abilities [7, 8].

The pharmacodynamics of bitter leaf extracts have also been reported in *vivo* experimentations with rats: Ugbogu *et al*. [2], while evaluating the phytochemistry, ethnobotanical, and pharmacological potentials of *V. amygdalina*, reported the anti-hepatoprotective effects of

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bitter leaf extracts on experimental mice with liver disorder induced by acetaminophen. The extract was also reported to have enhanced the antioxidant potency of certain enzymes against carbon tetrachloride (CCl4) given to mice. Bitter leaf extracts exhibited hepatoprotective effects synergistically with certain drugs, including isoniazid and rifampicin, in the mice. Bitter leaf extract generally demonstrated its ability to protect the liver and kidney against the deleterious effects of heavy metals and liver enzyme depletion, such as aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase, etc. A combination of bitter leaf and red sorrel extracts with ascorbic acid showed hepatoprotective activities against rat disease conditions caused by gamma radiation (4 Gy) [2]. A combination of vitamin C and bitter leaf extracts was reported to deplete the volume of alkaline phosphatase and lipid peroxidation (LPO) [24]. These activities have been reported to be powered by the flavonoid and saponin constituents present in bitter leaf extracts [7, 20].

The therapeutic efficacy of bitter leaf has also been widely demonstrated by several studies, which have evaluated its potential medicinal applications. In the work of Yunusa et al. [25] on the cytotoxic and the genotoxicity evaluation of *V. amygdalina,* the presence of alkaloids and flavonoids in the extract of bitter leaf reportedly had immunomodulatory properties which elevated immune responses and formed a shield against gastric ulcers. Many researchers like Edo *et al*. [7] and Egharevba [26] reported strong anti-parasitic activities of bitter leaf extracts which have the ability to fight against certain protozoan diseases such as leishmaniasis, malaria, and trypanosomiasis; they stressed that the presence of terpenoids in bitter leaf extract slowed down the metabolic processes of the cell membrane, proteins and the mitochondria of the parasitic organisms. A notable decrease in parasite density of *Plasmodium berghei* was further reported in malaria-infected mice after administration of bitter leaf extract, hence highlighting the anti-malarial abilities of the aqueous and acetone-water extracts of bitter leaf leaves and roots [2]. The presence of saponin compounds, dioscin, gracillin, and pseudo-protodioscin in bitter leaf extract has been reported to have anti-rheumatic properties [27].

Bitter leaf extract has demonstrated its ability to decrease lipid serum (triacylglycerol) levels, lower blood pressure, increase blood clotting abilities as well and control immune response; these abilities are attributed to the tannins contents of the bitter leaf extract [7, 28]. Bitter leaf extract also demonstrated its ability to reduce obesity in rats treated with obesity-generating substances. Ugbogu *et al* [2] reported a significant decrease in body weight and cholesterol in the brain, as well as a reduction in insulin and leptin after the administration of bitter leaf extract to the model organism.

The anti-diabetic properties of the bitter leaf have been extensively investigated, with numerous studies revealing its potential in managing both type 1 and type 2 diabetes [2, 12, 29]. Bitter leaf extracts have been shown to significantly reduce diabetes in mice induced with streptozotocin (STZ) [12]. Furthermore, phytochemical compounds isolated from bitter leaf stem-bark, namely 6β,10β, 14β-trimethylheptadecan-15α-oyl-15-O-β-Dglucopyranosyl-1,5β-olide, have been found to lower glucose levels in rats with STZ-induced hyperglycemia [29]. In the same vein, hot water extracts of bitter leaf have been shown to inhibit α-glucosidase activity and enhance insulin secretion by stimulating β-cell activity [2, 12, 29]. The synergistic anti-diabetic effects of bitter leaf extract have also been demonstrated in combination with metformin, resulting in improved glucose control in mice with alloxan-induced hyperglycemia [12]. Moreover, a decoction of African basil and bitter leaf has been found to reduce blood glucose levels in diabetic rats [2, 12, 29].

Some researchers have also reported the purgative potentials of bitter leaf extract. Ugbogu *et al*. [2] reported the cathartic activity of bitter leaf extracts, while mice fed with charcoal meal experienced constipation, but on the administration of bitter leaf extract, there was a speed-up of catabolic process within the mice, which caused it to have a bowel movement; thus, releasing feces. Nitrobenzene was reportedly used to cause neurological disease in rats and was treated with bitter leaf extracts in methanol afterward; the results revealed its ability to enhance neuronal growth and health [30]. Studies have also uncovered bitter leaf extract's anti-diarrheal properties; diarrhea was induced in mice by exposing it to castor oil, *Vibrio cholera,* but after the administration of bitter leaf extract, there was a significant improvement in the stoppage of the diarrhea [2, 31].

Interestingly, a study conducted by Ugogbu

et al. [2] revealed that the administration of bitter leaf extracts to HIV-positive patients undergoing anti-retroviral therapy resulted in a significant increase in lymphocyte levels. Notably, the lymphocyte count was found to be dose-dependent, with higher concentrations of bitter leaf extracts yielding greater increases in lymphocyte levels. Again, the study also indicated an enhancement in immune cell levels, suggesting a potential immunomodulatory effect of bitter leaf extracts in HIV-positive individuals.

Based on scientific evidence, bitter leaf extract's vast pharmacological properties have been attributed to its numerous phytochemicals and bioactive compound contents; it is also worth noting that the method of extraction contributes to the efficacy of the extracts.

Vernonia amygdalina extracts have been shown to be therapeutic in female health: it has been reported to have uterine contraction abilities in both humans and model organisms [38, 39], as well as used in the treatment of polycystic ovarian syndrome (PCOS) in female Wistar rats [40]. Attah *et al.* [38] reported that freshly squeezed bitter leaf extract administered to women during labor aided easy labor progression, strengthened or toned the uterus muscle, and prevented complications such as pain and bleeding. Among all other plant extracts used, bitter leaf extracts yielded the highest uterine contractility of 28.3 % at 150 minutes. The contractile effect was reported to last for 2.5 to 3.5 hours, suggesting that bitter leaf extract exhibits uterotonic activity, which may facilitate easy and uncomplicated labor in humans by enhancing uterine contractions. In the work of Ijeh *et al.* [39] on the effect of leaf extracts of *Vernonia amygdalina* on the contraction of the mammary gland and uterus of guinea pigs, they reported that the extracts of bitter leaf contain a potent uterotonic agent that induced uterine contraction amplitudes in guinea pig at 100 mg/ml. They also reported that the guinea pigs exposed to varying concentrations of bitter leaf extracts produced more milk than the control groups of guinea pigs.

These assertions authenticate the reasons why traditional healers and midwives in maternity clinics and rural communities use herbal remedies to speed up contractions and childbirths.

In another study with Wistar rats, Adedoun *et al.* [40] reported that after administering extracts of bitter leaf for 14 days to female Wistar rats with PCOS, there was a significant reduction of insulin and luteinizing hormone levels, increased follicle-stimulating hormone and progesterone levels when compared with the PCOS untreated group. They also reported the reduction of Serum IL-6, CRP, and TNF-α levels in the treated group when compared with the untreated group. A significant reduction in malondialdehyde level was also reported, as well as a significant reduction in triglycerides and LDL-C levels in the bitter leaf extract-treated rats.

Therapeutic Applications

The pharmaceutical potentials of bitter leaf extracts have been extensively investigated and substantially documented in various therapeutic applications (traditional, modern, and nutraceutical); these are attributed to their unique phytochemical profile and pharmacological properties. Bitter leaf has been deployed to cure several diseases such as fever, malaria, gastrointestinal conditions, respiratory ailments, skin infections, wounds, and so on, especially in Africa and Asia, for many decades as traditional medicine. Various formulations used were infusions, decoctions, and topical [5, 9, 13]. Notably, bitter leaf has gained positive recognition as a *novel* pharmaceutical lead, showing a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, anticancer, hepatoprotective, and immunomodulatory abilities [9, 13, 20, 22, 25]. Thus, according to Li *et al.* [4], the bitter leaf has been incorporated into food in the form of dietary supplements, functional foods, herbal teas, capsules, or tablets, providing certain nutraceutical advantages such as antioxidant effects [36], anti-inflammatory impacts, immune system assistance, and digestive enhancement.

Additionally, bitter leaf extracts has demonstrated strong effects against hypertension when evaluated using laboratory mice, even producing high level of synergistic activity in combination with *Ocimum gratissimun* (African basil) [7]. Some studies have affirmed bitter leaf's ability to reduce surplus calories and fat [2, 7]. Bitter leaf's bioactive compound (elotides), a hormone balancing compound enables it boost the fertility of women [2].

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The Bitter Taste of Bitter Leaf and Chloroquine: Pharmaceutical Implication

The bitter taste shared by bitter leaf and chloroquine is a result of the similar chemical structures they possess; alkaloids are partly responsible for the bitter taste. Alkaloids in bitter leaf and chloroquine possess antimicrobial properties [9, 13, 20]. Both have played critical roles in the treatment of human ailments for a long time. Chloroquine is a well-known anti-malarial drug, while bitter leaf has shown potential for anti-malarial properties [5, 25]. Regarding their taste, both activate bitter taste receptors in the tongue, thereby triggering a bitter sensation [32]. Structurally, chloroquine is C18H26ClN3 [33], while bitter leaf alkaloids (vernoline) are C21H25NO4 [9]. Chloroquine's structure consists of a quinoline ring, a chlorine atom, and a side chain containing two nitrogen atoms [33]. This quinoline ring plays a vital role in its anti-malarial properties [34]. Chlorine atom contributes to its pharmacological properties, including antimicrobial and anti-inflammatory effects [35]. On the other hand, bitter leaf alkaloid is (e.g., vernoline, C21H25NO4); the structure of vernoline comprises a sesquiterpene lactone ring, a nitrogen atom, and four oxygen atoms. According to a study, the antimicrobial and anti-inflammatory properties exhibited by vernoline are thought to be due to the presence of a sesquiterpene lactone ring [9]. Yunusa et al. [25], in their findings, suggested that the presence of four oxygen atoms in vernoline may play a role in its antioxidant effects. Consequently, the interesting pharmaceutical implications are significant. It impacts its anti-malarial property, attributing it to the quinoline ring component of chloroquine, suggesting that bitter leaf alkaloids may demonstrate similar anti-malarial effects driven by the presence of their sesquiterpene lactone ring [34].

Secondly, the antimicrobial and anti-inflammatory activities reveal that chloroquine and bitter leaf alkaloids display antimicrobial and anti-inflammatory activities because of their nitrogen-containing rings [9, 35]. Furthermore, the antioxidant abilities maintained by the bitter leaf's structure of alkaloids are probably due to being rich in oxygen, which might play a vital role in their antioxidant effects, making them different from chloroquine [25]. Regarding drug design and development, novel anti-malarial and antimicrobial agents may be possible by rigorously investigating the structural analogies and differences between chloroquine and bitter leaf alkaloids. It was noted in some studies that well-defined chemical structures may affect the pharmacokinetics and pharmacodynamics of chloroquine and bitter leaf alkaloids, influencing their bioavailability. [9, 20].

Summary of a critical analysis of the studies cited in this review article

The researchers seem to have done rigorous studies over the years covering the various aspects of bitter leaf's pharmaceutical prospects; however, there appear to be gray areas that need some attention; they are as listed below:

a. Methodological limitations

i. Lack of standardization: Many studies used different extraction methods, solvents, and concentrations, making it challenging to compare results.

ii. Limited sample sizes: Many of the studies had small sample sizes, reducing the precision of the results while broadening the margin of error in their studies.

iii. *In vitro* and *in vivo* studies: While *in vitro* studies provide valuable insights, more *in vivo* studies are necessary to confirm the efficacy and safety of bitter leaf extracts in humans.

b. Pharmacological properties

i. Antimicrobial activity: The antimicrobial activities of bitter leaf extracts against various micro-organisms are well documented. However, the mechanisms of action and the specific compounds responsible for this activity require further investigation.

ii. Anti-inflammatory activity: Bitter leaf extracts have shown anti-inflammatory activities in various studies. However, the specific compounds responsible for this activity and the underlying mechanisms require more investigation.

iii. Anti-cancer activity: The anti-cancer activities of bitter leaf extracts have been reported in several studies, although the specific compounds responsible for these activities have not been elucidated; thus, further investigations are needed to pinpoint the proteins and bioactive compounds of interest so that they can be isolated and used for pharmaceutical drug preparation at scale.

c. Therapeutic applications

i. Traditional medicine: Bitter leaf has been used in traditional medicine for various purposes. However, the efficacy, adequate dosage and safety of these uses require further investigations.

ii. Modern medicine: Bitter leaf extracts have shown potential in modern medicine, particularly in the treatment of infectious diseases, cancer, and inflammatory disorders. However, further research is necessary to confirm the efficacy and safety levels of their uses.

iii. Nutraceuticals: Bitter leaf extracts have been incorporated into food products and dietary supplements. However, the safety, dosage, and efficacy of these products require further investigation.

Future research directions on bitter leaf's pharmaceutical potential

In order to fully exploit the pharmaceutical potential of bitter leaf and unlock its broad therapeutic applications, future research should focus on the isolation and characterization of its bioactive compounds, pharmacokinetics and pharmacodynamics studies of bitter leaf-based products, clinical trials for the efficacy and safety dosage of bitter leaf based-products, toxicity and biosafety of bitter leaf based-products, and Regulatory guidelines (Figure 3).

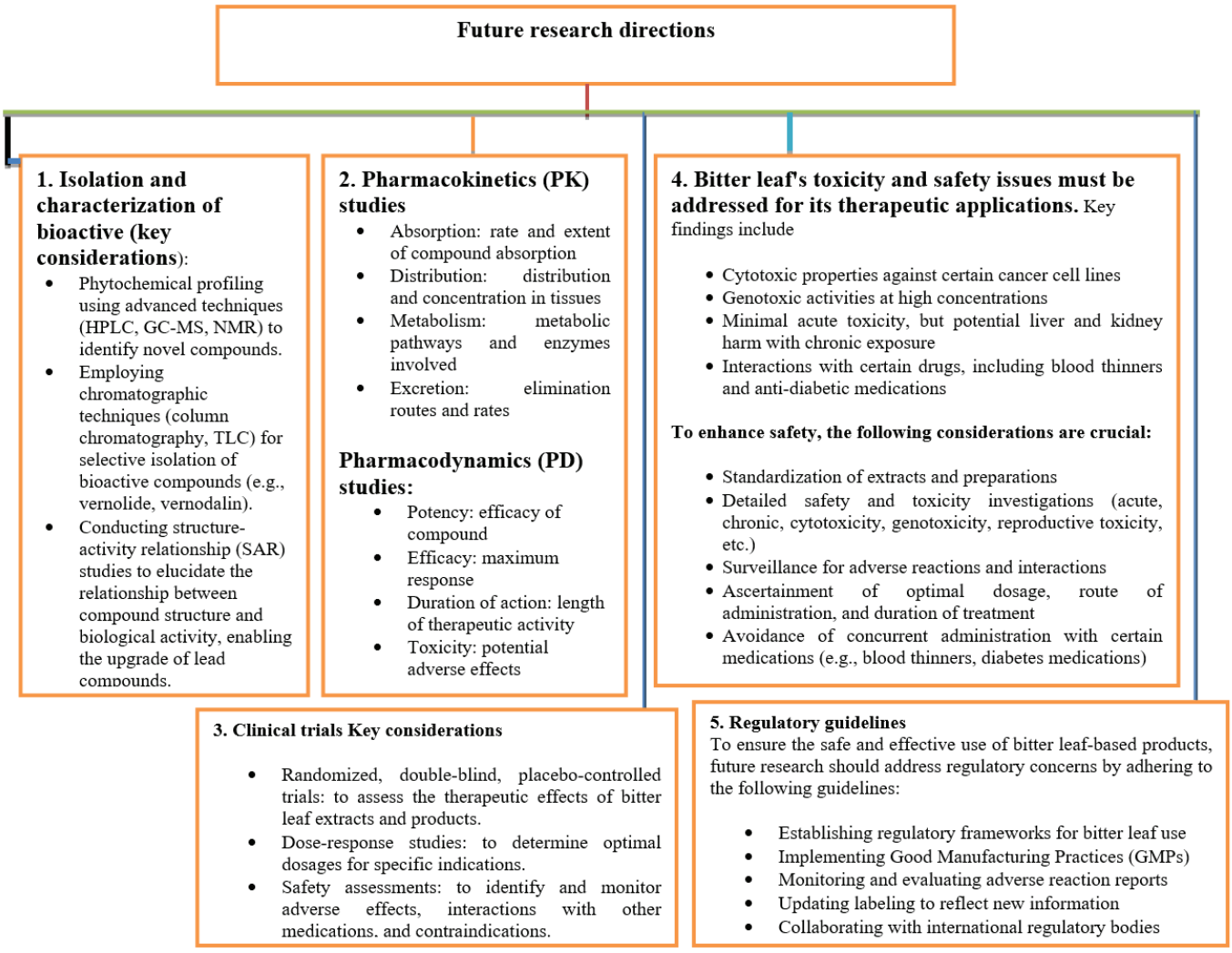

Figure 3: Future research focuses on the pharmaceutical potentials of bitter leaf

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Challenges and Opportunities

The major obstacles and prospects in tapping bitter leaf's full pharmaceutical potential are scalability and sustainability (scalability and sustainability entail producing bitter leaf-based products in large quantities without reducing the product's quality or environmental sustainability), regulatory frameworks (policy formulation and implementation for the regulation and standardization of bitter leaf-based products), and patent and intellectual property (protecting *novel*/native knowledge and inventions).

3. Conclusion

Vernonia amygdalina, generally known as a bitter leaf, has drawn notable recognition for its tremendous pharmaceutical potential. This review has comprehensively examined several bioactive compounds and pharmacological effects of bitter leaf, highlighting its potential as a therapeutic agent. Bitter leaf contains many bioactive compounds, including alkaloids, flavonoids, terpenes, and sesquiterpene lactones. However, further research is necessary to confirm the efficacy and safety of bitter leaf extracts in humans. Standardization of extraction methods, solvents, and concentrations is essential to ensure consistency in results. Additionally, *in vivo* studies and clinical trials are necessary to confirm the therapeutic potential of bitter leaf extracts.

Ethics approval
Ethics approval is not applicable; a review article.

Consent to participate
It does not apply to a review article.

Consent for publication
The authors have given their consent for the article to be published.

Availability of data and materials
As synthesized from databases.

Competing interests
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