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Biological and bioactive components of bitter leaf (*Vernonia amygdalina* leaf): Insight on health and nutritional benefits. A review

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ABSTRACT

Recently, significant attention has been paid to the biologically active substances in plants that aid in preventing, treating or delaying diseases brought on by inflammatory and oxidative processes. There is scientific evidence to support the use of plant extracts in traditional medicines to treat bacterial, protozoal, and helminthic illnesses. From the leaf of *Vernonia amygdalina* also, phytochemicals have been identified and extracted, including alkaloids, tannins, steroids, cyanogenic glycosides, flavonoids, phenolic acids, lignans, xanthones, anthraquinones, oxalate and saponins. This article provides a comprehensive overview of the bioactive components of bitter leaf and how they contribute to its medicinal properties. Its health benefits; including its ability to lower cholesterol levels, it's anticancer and antioxidant properties as well it's potential as a natural remedy for diabetes are also discussed. Conclusively, the article underscores the significance of drinking bitter leaf juice and the effects it has on health and wellness.

1. Introduction

The varieties of medicinal plants found worldwide particularly those that exhibit a wide range of health remedying properties have caught the interest of researchers (Farombi & Owoeye, 2011). Bioactive compounds contained in these plants account for the distinct physiological activities they effect on the human health that make them an interest to these researchers (Ugbogu et al., 2021). Moreover, it is estimated that more than 80 % of people use herbal products either as dietary supplements (Hassan et al., 2021), alternative medicines or as nutraceuticals (Thakkar et al., 2020).This is primarily because the bioactive constituents of these plants account for antioxidant, antibacterial, antidiabetic, antihemlmintic, anticancer, antiasthma, antiparasitic and etcetera effects which they exhibit (Tungmunnithum et al., 2018). In the tropical regions of Africa, one such existing medicinal plant is Vernonia amygdalina; a perennial shrub commonly known as bitter leaf plant due to the bitter taste of its leaves. The plant originates from the Asteraceae (compositae) family and usually presents as a shrub of about 2.5–3 m height (Achuba, 2018). Some few cases though have reported tall V. amygdalina trees of 7 m (Farombi & Owoeye, 2011). V. amygdalina has a rough bark with dense black straits, it comprise of green colored elliptic leaves that have a characteristic odor and bitter taste (Akpoghelie et al., 2022). V. amygdalina goes by other African names as well for example; ewuro (Yoruba), etidot (Efik), ityuna (Tiv), Congo Bololo (D. R. Congo), oriwo (Edo), onugbu (Igbo), grawa (Amharic), shuwaka or chusar-doki (Hausa), Awɔnwono (Akan), mululuza (Luganda), olusia (Luo) and labwori .The V. amygdalina leaf itself which happens to be the subject of our review has been proven to contain significant quantities of lipids (Adaramoye, 2008), carbohydrates, proteins having high essential amino acid scores (Edo et al., 2022), fiber, iron, phosphorous, copper, calcium, potassium, cobalt and manganese, appreciable amounts of biologically active compounds like ascorbic acid, saponins, alkaloids,

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steroids terpenes, flavonoids, coumarins, lignans, phenolic acids, edotides, xanthones, anthraquinone, sesquiterpenes and caroteinoids (Erhonyota et al., 2022). Extracts from bitter leaf can be used as tonics to treat a variety of ailments and maladies, including emesis, nausea, diabetes, anorexia, diarrhea, dysentery and other gastrointestinal tract issues (Adebukola Adeyanju et al., 2022) which explains why many herbalists and indigenous doctors in Africa recommend that their patients take the aqueous preparations of these leaves against certain health maladies (Usai et al., 2022). Studies have also revealed that some compounds found in bitter leaves like vernodalin and vernonioside, can inhibit the activity of inflammatory enzymes like COX-1 and COX-2 and also suppress the production of pro-inflammatory cytokines like IL-1β, TNF-α and IL-6 (Farombi & Owoeye, 2011), thus leading to a reduction in pain and inflammation and by that, positing bitter leaf as a potential treatment for varieties of inflammatory conditions like arthritis, asthma etcetera (Sweis & Cressey, 2018). In addition to anti-inflammatory properties, bitter leaf extracts have also been found to possess antioxidant properties (Iruoghene Edo, 2022). The antioxidants present in bitter leaf are able to neutralize harmful free radicals which usually contribute to tissue damage (Edo et al., 2023). Furthermore, the organic extracts from bitter leaf have also been demonstrated to exhibit cytotoxic effects on human nasopharyngeal cancer cells (Hussain et al., 2022). This makes them a potential treatment for conditions like cancer, diabetes and liver diseases (Singh Makhaik et al., 2021). The antimicrobial properties of the extracts of this leaf also give it a place for use as treatment against a wide range of infections seeing that the extracts was once reported to demonstrate inhibitory actions on bacteria, fungi and viral microorganisms (Ugbogu et al., 2021). Little wonder then that Chimpanzees in the wild are seen to consume these leaves when they have parasite infections (McLennan et al., 2017). Bitter leaf is also known to have benefits on the reproductive health as studies have reported it to both increase sperm count and improve its quality in men (Trendafilova et al., 2020).Bitter leaf is likewise believed to have benefits for women's reproductive health as it helps to regulate menstrual cycles and ease symptoms of premenstrual syndrome (Owheruo et al., 2023). A long history of culinary and traditional uses has been linked to bitter leaf; take the country Nigeria for instance where the leaves are used as a green vegetable in the popularly known bitter-leaf soup. In preparing this soup, bitter leaves harvested from plant are macerated in cold water or are boiled to bring the bitterness to a tolerable level; other seasonings are then added to complete the soup (Alara et al., 2019). Bitter leaf can also be used traditionally as an appetizer and the aqueous extracts as digestive tonics (Ugbogu et al., 2021). The leaves have also been seen to be effective against fevers so much so that they are used as a substitute for quinine. Furthermore, bitter leaves in some parts of Nigeria (northern parts) are added to horse feed to serve for fattening and strengthening of the animals (Farombi & Owoeye, 2011). In folk medicine also, the young leaves serve against hermitic infections, as purgatives, expectorants and as a fertility inducer in unfertile women. (Olusola-Makinde et al., 2021). Nowadays, the availability of bitter leaves in supplement forms makes it easy for people to incorporate it in their daily diets. However, it is important to consult with a healthcare professional before using bitter leaves as a treatment for any health condition (Sofowora et al., 2013). This review aims to provide a comprehensive overview of the bioactive components of the said leaf, discuss its biological activities and the benefits that can be derived from drinking its juice.

2. Methodology

The scientific papers for this review were retrieved from Science direct (https://www.sciencedirect.com), Goggle Scholar (https://scholar.google.com/), research gate (https://www.researchgate.net) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases. The keywords used were both medical headings and free text "bioactive compounds in bitter leaf", "Anticancer activities associated with bitter leaf", "composition of bitter leaf", "benefits of drinking bitter leaf juice", "traditional uses of bitter leaves", "tannins" "classes of saponins", "subgroups of flavonoids" "terpenoids found in bitter leaf" "antioxidant activity of bitter leaf" "antidiabetic properties of bitter leaf" "can bitter leaf induce weight loss" "cholesterol lowering properties of bitter leaf" " how does bitter leaf improve digestion"

3. Composition of bitter leaf

The distribution of biologically active compounds in bitter leaf has not been fully established but in general, bitter leaves are rich in nutrients like proteins (up to 20 %), lipids (4.7 %), iodine (35.8 mcg), copper (6–10 mg/100 g), iron (5.14 %), vitamin A and E, thiamine and also a good amount of reducing sugars are present in the leaves. Phytochemicals like saponins, coumarins, flavonoids, lignans, alkaloids, xanthones are also present in the leaf, stem and roots of *Vernonia amygdalina*. (Egharevba, 2014). Fig. 1(a) shows a pictorial representation of *V. amygdalina* plant and (b) shows the washed bitter leaves. The nutritional and phytochemical components of the plant are also shown in Tables 1 and 2, respectively.

3.1. Bioactive components of bitter leaf

3.1.1. Terpenoids

Terpenoids are a large class of organic compounds which have unsaturated molecules that are made up of linked isoprene units. They include terpenes, ses quiterpenes and diterpene (Masyita et al., 2022). Experimental proofs from many bioassays agree that terpenoids have therapeutic potentials against diseases caused by protozoa such diseases as leishmaniasis, malaria and trypanosomiasis (Ugbogu et al., 2021). Other reports indicate that the mechanisms by which terpenoids exhibit these antiparasitic activities. They are; (1) through interfering with mitochondrial respiration, (2) interacting with various significant proteins in the parasites and (3) disrupting the architecture of the parasite cell membrane (Egharevba, 2014). The terpenoids; sesquiterpene lactones (vernolide, vernolepin, vernodalinol, hydroxyvernolide, vernolic, vernodalin, vernomenin, vernomydin) are thought to be connected with bitter leaf's ability to regulate blood glucose (Owheruo et al., 2023).

3.1.2. Tannins

Tannins (sometimes called tannic acid) are sophisticated chemicals generated from phenolic acids. They are a group of astringent polyphenolic biomolecules that precipitate proteins as well as a variety of other organic substances such as amino acids and alkaloids, when bond to them (Edo et al., 2023). The term "tannins" itself is generally used to refer to any big polyphenol substance that has enough hydroxyls and other appropriate groups to form robust complexes with macromolecules (Edo, 2022a). Tannins are present in a wide variety of plant species from all climatic zones and geographical regions (Kumar et al., 2017). Like many other polyphenols, tannins function as antioxidants, assisting in preventing and or repairing cellular damage brought about by the attack of free radicals (Rudrapal et al., 2022). Tannins are divided into two groups: hydrolyzable tannins and condensed tannins. Hydrolyzable tannins are the type that can be hydrolyzed by an acid or an enzyme to yield ester-like compounds which are polymers of ellagic and garlic

Fig. 1. (a) Bitter leaf plant (b) washed bitter leaves.

Table 1
Nutritional composition of Bitter leaf.

Carbohydrate (mg/100 g)	Protein	Vitamins (mg/100 g)	Minerals
Sucrose 13.20	Hydrolysate -	Riboflavin 3.10	Potassium -
Glucose 7.20	Casein 96.99	Ascorbic acid 20.4	Magnesium 88.1
Fructose 6.0	Cysteine 1.84	Nicotinamide 0.41–1.65	Sodium 8.5
Galactose 6.56	Glycine 4.63	Thiamine 100–170	Calcium 67.27
Lactose 2.61		Carotenoids 30	Zinc 8.05
Maltose 7.24		Vitamin E 106.20	Iron 5.0
Arabinose 9.25		Vitamin A 30.90	Iodine (ug/100 g) 35.82

Table 2
Phytochemical composition of *V. amygdalina* in roots, stems and leaves.

Compound	Root	Stem	Leaf
Steroid	1.9	–	0.38
Oxalate	3.5	1.8	0.62–5.38
Tannin	22.10	6.0	9.62
Flavonoid	0.5	1.0	4.89
Saponin	28.5	13.21	1.425
Cyanogenic glycoside	1.40	1.28	1.11
Phenol	2.34	6.87	3.24
Anthraquinone	2.0	0.8	0.14
Alkaloids	6.9	7.0	2.2
Polyphenols	15.0	11.0	9.76
Total phenolics	42.63	25.0	156.4

acids (Lisak Jakopović et al., 2022). Anti-angiogenic, anti-cancer, anti-oxidant, anti-ulcerative and anti-inflammatory properties are exhibited by hydrolysable tannins (Jikah & Edo, 2023). Condensed tannins on the other hand are derived from catechins and flavan-3,4-diols and are usually resistant to hydrolysis. They compounds instead, re-decompose into phlobaphenes upon treatment with acids or enzymes (Edo et al., 2023). In this group of tannins also, the nuclei are held in place by ether or carbon-carbon linkages. Animals have been benefited by condensed tannins through improved fertility, increased milk and wool production. Cinchona bark, male fern, areca seeds, tea leaves, wild cherry bark, behera fruit, Amla, and other plants contain condensed tannins (Edo et al., 2022). Tannin molecules have demonstrated ability to decrease the mutagenic activity of some mutagens (Ademiluyi et al., 2023). Oxygen-free radicals are created by some carcinogens or mutagens by means of which they interact with cellular macromolecules therefore, the anticarcinogenic and antimutagenic properties of tannins may be traceable to their antioxidative potential against these oxygen-free radicals. This activity is important in protecting the cells from oxidative damage and lipid peroxidation (Edo et al., 2023). Tannins were also reported to inhibit the generation of superoxide radicals and their related compounds and in like manner, inhibit the growth and development of yeasts, fungi, bacteria and viruses thus attesting to their antimicrobial capacities (Edo, 2022b). Tannic acid was at another instance also discovered to have inhibitory actions against food-borne bacteria, off-flavor-producing microorganisms and aquatic bacteria (Ademiluyi et al., 2023). This antimicrobial property can be employed in food processing to lengthen the shelf-life of certain foods, like catfish fillets (Achuba, 2018). Hastening the clotting of blood, decreasing serum levels of lipids, reduction of blood pressure, modulation of immune-response have all been reported about tannins although the type and the dosage of tannin given are vital for these effects (Sofowora et al., 2013).

3.1.3. Saponins

Saponins are naturally occurring substances that are found in large quantities throughout cells of leguminous plants. In plants, their anti-fungal, anti bacteria, anti-parasitic effects make them suitable for the defense needs of the plant, defending against infections and microbial attack. These complex and diverse collection of chemicals get their name from their capacity to create stable, soap-like foams and emulsions in aqueous medium. Their amphipathic structure, which includes a hydrophobic aglycone backbone and a hydrophilic glycan component, makes this possible (Ashour et al., 2019). As versatile glycosidic compounds possessing several biological properties (anti- hyperglycemic, anti-inflammatory, hypocolesterolemic anti-oxidant and anti-tumor properties), saponins have been employed for different applications in the pharmaceutical sector (one such application is the use of saponins by this industry as an initiative precursor for the semi-synthesis of steroidal drugs) (Semerdjieva & Zheljazkov, 2019). Furthermore, the dioscoresides contained in saponins make their use in the treatment and prevention of cerebrovascular and cardio diseases appropriate (Larayetan et al., 2019). Other saponin compounds like dioscin, gracillin and pseudo-protodioscin are used as anti- rheumatic treatment (Kunnumakkara et al., 2023).

3.1.4. Alkaloids

An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state. Alkaloids have a wide range of physiological effects, including antibacterial, antimitotic, antiinflammaty, analgesic, local anesthetic, hypnotic, psychotropic, and anticancer activities (Jan et al., 2021). Alkaloids (morphine, quinine, ephedrine e.t.c) are useful in dietary supplements and medications. They are also a crucial component of organic synthesis (Dey et al., 2020). 20 alkaloids were found in bitter leaves according to Abay and his team's investigations. The range was from 0.03 % to 34.00 %. Therefore they suggested that if taken in sufficient quantities, bitter leaves may be highly beneficial in the treatment of illnesses that affect both humans and animals.

3.1.5. Flavonoids

Flavonoids are a class of naturally occurring molecules with varying phenolic structures (Samje et al., 2014). Dietary flavonoid compounds can be found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. The bitter leaf plant has been observed to produce flavonoids, in response to microbial infection (Samje et al., 2014). But in addition to being relevant to the plant, the flavonoids are significant for human health owing to their powerful pharmacological effects, (Mainka et al., 2021) they have a variety of beneficial biochemical and antioxidant properties against a number of illnesses, including cancer, Alzheimer's disease (AD), atherosclerosis, etcetera (Semerdjieva & Zheljazkov, 2019). Other evidences exists which suggest that flavonoids have free radical scavenging, coronary heart disease prevention, hepatoprotective, anti-inflammatory properties and antiviral properties (Nwaoguikpe, 2010). Luteoin 7–0-glucoronoside is an example of a flavonoid in bitter leaf.

Flavonoids have various subgroups that can be distinguished from each other based on their structural characteristics (Edo et al., 2023). These subgroups include chalcones, flavones, flavonols, isoflavones and flavanones. Table 3 shows some health benefits of flavonoids contained in bitter leaf.

4. Biological properties of bitter leaf

4.1. Antioxidant activity

Free radical-scavenging abilities of medicinal plants have been employed in order to moderate the actions of electron-deficient molecules like free radicals in the body. Free radicals otherwise known as reactive oxygen species like the hydroxyl (OH) radical, superoxide (O_2), nitric oxide (NO), nitrogen dioxide (NO_2), and hydrogen peroxide (H_2O_2) are molecules with an electron shortage and in their search for electrons, can easily assault bodily cells leading to the development of illnesses (Phaniendra et al., 2015). The occurrence of several

Table 3
Some health benefits of flavanoids contained in bitter leaf.

Health benefits	Activity	Refs.
Anticancer effects	They influence the activities of enzymes that scavenge reactive oxygen species (ROS), participate in cell cycle arrest, trigger apoptosis and autophagy, and inhibit the growth and invasiveness of cancer cells.	Perillo et al. (2020)
Cardiovascular system	Due to the benefits of lowering blood pressure, reducing lipid oxidation, and increasing endothelial function, a diet high in flavonoids can lower the incidence of ischemic strokes.	Guo et al. (2022)
Nervous systems	The blood flow to the brain and sensory systems can to be improved by flavonoids, which also have positive effects on the peripheral and central nervous systems.	Zeli et al. (2022)

pathological conditions like cell damage due to lipid peroxidation, DNA damage, and cellular degeneration have all been liked to these compounds (Sharifi-Rad et al., 2021). Free radicals can be combated by molecules known as antioxidants and these antioxidants are compounds with sufficient electrons which are ready to donate to the free radicals. In Bitter leaf, flavonoids namely: luteolin, luteolin 7-O-βglucuronoside, luteolin 7-O-β-glucoside have been reported to exhibit antioxidant activities against radicals. (Farombi & Owoeye, 2011). A comparison of the three flavones' antioxidant activity revealed that luteolin outperformed the other two in antioxidant activity. Furthermore, oxidative stress was studied in diabetic rats using the aqueous extracts of bitter leaf. Serum levels of malondialdehyde were seen to be decreased showing antioxidant property (Owolabi et al., 2011). Yet another study showed further that even the ethanolic extracts of bitter leaves possess potent antioxidant properties as they inhibited β-carotene bleaching, linoleic acid oxidation and Fe2+/ascorbate-induced lipid peroxidation in rat liver microsomal experimentations (Chisté et al., 2014). The antioxidant activities of the extracts by ethanol of the leaves were observed to be higher than those of the aqueous extracts (González-Palma et al., 2016). Antioxidants are also used as preservatives for increasing the shelf life of food products (Edo et al., 2023).

4.2. Anticancer properties

Globally, the burden of cancer has become a serious problem with breast and prostate cancers been the most diagnosed non-skin cancers in women and men respectively. Prostate cancer represents 15.3 % of all cancers in men while breast cancer represents 15 % of all novel cases of cancers in developed countries (Sung et al., 2021) the need therefore for botanicals or phytotherapeutics that show efficacy against different cancers to be urgently developed is presented (Nwosu et al., 2022). The anticancer potential of bitter leaf is thought to be linked with its coumarins, edotides, flavonoids and sesquiterpenes lactones contents. A study showed that the chloroform extracts and the bioactive peptides (edotides) obtained from the aqueous extracts of bitter leaf both have potent anticancer properties as they show potency in managing cancer through actions on mitogen activated protein kinases and the signal transduction pathways (Sung et al., 2021).

Bitter leaf was also seen to significantly reduce the viability of MCF-7 breast cancer cells in a dose-dependent manner and thus inducing DNA damage in the said cells (Howard et al., 2015). These results were in sync with the results obtained by Iruoghene Edo (2022) where the water-soluble fractions of bitter leaf were seen to inhibit DNA synthesis and the growth of BT-549 cancer cells in a dose-dependent manner. Using the hexane, chloroform, butanol and ethylacetate extracts of the leaves too, inhibition of growth in human breast cancer cells at doses of 0.1–1 mg/ml was observed. With bitter leaf's utilization in the management of breast cancer now been established, its effectiveness with other cancers ought to be studied as well (Wong et al., 2013).

4.3. Hepatoprotective properties

Liver problems are recognized as serious medical issues owing to the central role the liver plays in xenobiotic transformations and metabolic homeostasis (Casas-Grajales, 2015). A study found that weanling albino rats were protected against aflatoxin B1-induced hepatotoxicity by a diet incorporated with the bitter leaves (Iwo et al., 2017). Furthermore, another study found that bitter leaf extracts did not only protect against tetrachloromethane-induced hepatotoxicity, but they as well reversed the hepatic damages that occurred in the rats (Achuba, 2018).

4.4. Cholesterol lowering properties

Dyslipidemia is well known to be a risk factor for cardiovascular diseases. Synthetic pharmacological interventions used to modulate lipid levels often have lethal side effects (Berberich & Hegele, 2022). The search for alternatives that are less toxic, but which can perform the same tasks as the synthetic counterparts became essential (Maertens et al., 2021). Experiments with bitter leaves incorporated into diets were seen to lower serum triacylglycerol and LDL-cholesterol levels and as well to increase HDL-cholesterol levels (Abdulmalik et al., 2016). In an experiment with diabetic rats also, it was reported by Onyibe et al. (2021) that the aqueous extracts of bitter leaf normalized serum cholesterol concentrations and also reduced triacylglycerol levels. The extracts by ethanol of bitter leaf were as well seen to keep the lipid profile of rats within the normal range with doses of 100–1000 mg/kg body weight. These findings together with reports of the antidiabetic and antioxidant properties of bitter leaf suggest that it may take up a very important role in the management of chronic diseases in time to come.

4.5. Improvement of digestion

Bitter leaf contains a substance called quercetin, which has been demonstrated to help alleviate inflammatory bowel disease (IBD) (Ugbogu et al., 2021). This substance can also lessen inflammation in the gut since quercetin is a naturally occurring anti-inflammatory substance (Ighodaro et al., 2017). This may result in better gut health and reduced stomach discomfort. Bitter leaf in addition to having anti-inflammatory qualities is also a good fiber source (Iruoghene Edo, 2022) and fiber is crucial for gut health (Gadanya et al., 2021). Constipation and other digestive problems are avoidable with a diet rich in fiber.

4.6. Anti-diabetic properties

Diabetes mellitus is a metabolic disorder that is said to affect more than 200 million people globally. There are projections that it will affect 366 million persons by the year 2030 (Saeedi et al., 2019). Blood glucose is the body's main source of energy and comes from the food we eat (Wang & Wang, 2017). When the pancreas develops an inability to produce enough insulin or when the cells of the body resist insulin, glucose uptake by the cells is limited leading to increased amount of glucose in the blood (Drzewoski & Hanefeld, 2021). Approximately 2.2 million deaths are attributed to excessive blood sugar levels with an estimated 1.5 million deaths directly linked to diabetes every year (Al-Jawaldeh & Abbass, 2022). The use of drugs to treat diabetes mellitus can have negative side effects including weight gain, hypoglycemia, and an increased risk of cardiovascular mortality. These limitations of drug pharmacological therapies have led to the use of complementary therapies derived from plant extracts, the likes of bitter leaf as an anti-diabetic remedy. Bitter leaf extracts were reported to assist in the regeneration of pancreatic beta cells after they were artificially destroyed through streptozotocin induction (Patel et al., 2012). Promotion of the uptake of glucose by liver and muscle cells of the body was also observed with bitter leaf. Additionally, the aqueous extracts of bitter leaf were seen to give a significant decrease in the blood sugar

concentration of both normal and diabetic rats to an extent that was comparable to the results with chlorpropamide, the standard drug (Onyibe et al., 2021). With the extracts by ethanol of the leaves too, blood glucose lowering effects were observed in rats. Tell tailing that the active blood glucose decreasing compounds can be extracted using both polar and non-polar solvents (Edo et al., 2023). Bitter leaves at another instance were administered to normoglycamic humans and noteworthy postprandial blood sugar reduction effects were observed at 30 min intervals for 2 h. Studies should be conducted to see if these results can be obtained in diabetics.

5. Benefits of bitter leaf juice

5.1. Lowering of high blood pressure

In an experiment involving laboratory mice that suffered high blood pressure, aqueous extracts of bitter leaf was administered and a reduction of blood pressure was observed in the subjects as compared with the control group (Achuba, 2018). A second experiment showed that salt-induced hypertension could be managed by the synergistic effects of *V. amygdalina* leaf and *Ocimum gratissimum* (African basil) (Irondi et al., 2016). Yet another study involving cats was conducted from which the researchers concluded that the aqueous extracts of bitter leaves was effective against hypertension (Edo et al., 2023). Interesting to note is the fact that even at high doses bitter leaf is safe as no significant toxicity has been seen with its use (Egharevba, 2014).

5.2. Aiding in weight loss

Bitter leaf juice is a remedy for burning off excess fat. Excess calories can also be reduced by daily intake of bitter leaf juice (Ugbogu et al., 2021).

5.3. Enhanceing fertility

Bitter leaf extracts helps women's fertility issues (Ugbogu et al., 2021), research shows that drinking bitter leaf juice can aid in conception since it contains chemical compounds like edotides that support hormonal balance and strengthens the body's defenses against toxicity. The chances of getting pregnant increases naturally when the body's hormones are at equilibrium (Atashpour et al., 2017).

6. Conclusion

Bitter leaf is highly valued for the numerous bioactive properties and consequent biological activities it elicits. It has for instance been found to possess antioxidants by which it exerts its biological activities. In addition to antioxidants, the entire phytochemical profile of the leaf also contributes to its value as a natural resource for improving human health and wellness. Little wonder then it is applicable against numerous diseases like; cancer, anemia, diabetes, inflammatory disorders, microbial infections et al. This review highlights the vast potential of bitter leaf as a source of health benefiting phytochemicals and their applications against different diseases. It is however worthy of note that the widespread pharmacological activities of bitter leaf notwithstanding, further experimental and clinical research is still needed to fully understand the mechanisms of action by which these phytochemicals produce pharmacological actions as well as establish the safety and effective dosages.

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Not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable

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The authors have no competing interests.

Data availability

Data will be made available on request.

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References

Abdulmalik, O., Oladapo, O. O., & Bolaji, M. O. (2016). Effect of aqueous extract of Vernonia amygdalina on atherosclerosis in rabbits. *ARYA Atherosclerosis, 12*(1), 35–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27114735.

Achuba, F. I. (2018). Role of bitter leaf (Vernonia amygdalina) extract in prevention of renal toxicity induced by crude petroleum contaminated diets in rats. *International Journal of Veterinary Science and Medicine, 6*(2), 172–177. https://doi.org/10.1016/j.ijvsm.2018.07.002

Adaramoye, O. A. (2008). Lipid-lowering effects of methanolic extract of *Vernonia amygdalina* leaves in rats fed on high cholesterol diet. *Vascular Health and Risk Management, 4*(1), 235–241. https://doi.org/10.2147/vhrm.2008.04.01.235

Adebukola Adeyanju, A., Rebecca Oyenihi, O., & Omoniyi Oguntibeju, O. (2022). Antioxidant-rich vegetables: Impact on human health. *Vegetable crops - Health Benefits and cultivation*. Intechopen. https://doi.org/10.5772/intechopen.101126

Ademiluyi, A. O., Ogunsuyi, O. B., Akinduro, J. O., Aro, O. P., & Oboh, G. (2023). Evaluating Water bitter leaf (Struchium sparganophora) and Scent Leaf (Ocimum gratissimum) extracts as sources of nutraceuticals against manganese-induced toxicity in fruit fly model. *Drug and Chemical Toxicology, 46*(2), 236–246. https://doi.org/10.1080/01480545.2021.2021928

Akpoghelie, P. O., Edo, G. I., & Akhayere, E. (2022). Proximate and nutritional composition of beer produced from malted sorghum blended with yellow cassava. *Biocatalysis and Agricultural Biotechnology, 45*, Article 102535. https://doi.org/10.1016/j.bcab.2022.102535

Alara, O. R., Abdurahman, N. H., Ukaegbu, C. I., & Kabbashi, N. A. (2019). Extraction and characterization of bioactive compounds in Vernonia amygdalina leaf ethanolic extract comparing Soxhlet and microwave-assisted extraction techniques. *Journal of Taibah University for Science, 13*(1), 414–422. https://doi.org/10.1080/16583655.2019.1582460

Al-Jawaldeh, A., & Abbass, M. M. S. (2022). Unhealthy dietary habits and obesity: The major risk factors beyond non-communicable diseases in the Eastern Mediterranean Region. *Frontiers in Nutrition, 9*. https://doi.org/10.3389/fnut.2022.817808

Ashour, A. S., El Aziz, M. M. A., & Gomha Melad, A. S. (2019). A review on saponins from medicinal plants: Chemistry, isolation, and determination. *Journal of Nanomedicine Research, 7*(4), 282–288. https://doi.org/10.15406/jnmr.2019.07.00199

Atashpour, S., Kargar Jahromi, H., Kargar Jahromi, Z., & Maleknasab, M. (2017). Comparison of the effects of Ginger extract with clomiphene citrate on sex hormones in rats with polycystic ovarian syndrome. *International Journal of Reproductive Biomedicine, 15*(9), 561–568. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29662964.

Berberich, A. J., & Hegele, R. A. (2022). A modern approach to dyslipidemia. *Endocrine Reviews, 43*(4), 611–653. https://doi.org/10.1210/endrev/bnab037

Casas-Grajales, S. (2015). Antioxidants in liver health. *World Journal of Gastrointestinal Pharmacology and Therapeutics, 6*(3), 59. https://doi.org/10.4292/wjgpt.v6.i3.59

Chisté, R. C., Freitas, M., Mercadante, A. Z., & Fernandes, E. (2014). Carotenoids inhibit lipid peroxidation and hemoglobin oxidation, but not the depletion of glutathione induced by ROS in human erythrocytes. *Life Sciences, 99*(1–2), 52–60. https://doi.org/10.1016/j.lfs.2014.01.059

Dey, P., Kundu, A., Kumar, A., Gupta, M., Lee, B. M., Bhakta, T., et al. (2020). Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). *Recent*

advances in natural products analysis (pp. 505–567). Elsevier. https://doi.org/10.1016/B978-0-12-816455-6.00015-9
Drzewoski, J., & Hanefeld, M. (2021). The current and potential therapeutic use of metformin—The good old drug. *Pharmaceuticals, 14*(2), 122. https://doi.org/10.3390/ph14020122
Edo, G. I. (2022a). Antibacterial, phytochemical and GC–MS analysis of Thevetia peruviana extracts: An approach in drug formulation. *Natural Resources for Human Health*. https://doi.org/10.53365/nrfhh/146543
Edo, G. I. (2022b). Antibacterial, phytochemical and GC-MS analysis of Thevetia peruviana extracts: An approach in drug formulation. *Natural Resources for Human Health, 2*(4), 418–426. https://doi.org/10.53365/nrfhh/146543
Edo, G. I., Makinde, M. G., Nwosu, L. C., Ozgor, E., & Akhayere, E. (2022a). Physicochemical and pharmacological properties of palm oil: An approach for quality, safety, and nutrition evaluation of palm oil. *Food Analytical Methods, 15*(8), 2290–2305. https://doi.org/10.1007/s12161-022-02293-4
Edo, G. I., Onoharigho, F. O., Akpoghelie, P. O., Emakpor, O. L., Ozgor, E., & Akhayere, E. (2022b). Physicochemical, phytochemical, antioxidant, and inhibition properties of key enzymes linked to raw and regular honey. *Chemistry Africa*. https://doi.org/10.1007/s42250-022-00401-9
Edo, G. I., Samuel, P. O., Jikah, A. N., Oloni, G. O., Ifejika, M. N., Oghenegueke, O., et al. (2023a). Proximate composition and health benefit of Roselle leaf (Hibiscus sabdariffa). Insight on food and health benefits. *Food Chemistry Advances, 3*, Article 100437. https://doi.org/10.1016/j.focha.2023.100437
Edo, G. I., Samuel, P. O., Ossai, S., Nwachukwu, S. C., Okolie, M. C., Oghenegueke, O., et al. (2023b). Phytochemistry and pharmacological compounds present in scent leaf. A review. *Food Chemistry Advances*. , Article 100300. https://doi.org/10.1016/j.focha.2023.100300
Edo, G. I., Ugbune, U., Akpoghelie, P. O., & Owheruo, J. O. (2023). Evaluation of physicochemical, phytochemical, anti-bacterial and antioxidant potential of kola nut (cola acuminata): An approach in food, health and nutritional benefits. *Vegetos*. https://doi.org/10.1007/s42535-023-00715-0 (Bareilly, India).
Edo, G. I., Ugbune, U., Ezekiel, G. O., Nwosu, L. C., Onoharigho, F. O., & Agbo, J. J. (2023c). Medicinal plants used for the treatment of sexual dysfunction; ethnobotanical study and phytochemical analysis. *Acta Ecologica Sinica*. https://doi.org/10.1016/j.chnaes.2023.05.008
Edo, G. I., Ugbune, U., Onoharigho, F. O., Ezekiel, G. O., & Agbo, J. J. (2023d). Antioxidant activities of reissantia indica willd. (mopane paddle-pod) and nephroprotective effect on paracetamol-induced nephrotoxicity in male wistar rats. *Nutrire, 48*(1), 26. https://doi.org/10.1186/s41110-023-00214-x
Edo, G. I., Ugbune, U., Onoharigho, F. O., Ezekiel, G. O., Ugbuwe, E., & Agbo, J. J. (2023e). COordination of bioactive phytochemical from ginger extracts to metal ions; investigation of the metal complexes and bioactive compound formed. *Food Chemistry Advances*. , Article 100337. https://doi.org/10.1016/j.focha.2023.100337
Egharevba, C. (2014). Significance of bitter leaf (Vernonia Amagdalina) in tropical diseases and beyond: A review. *Malaria Chemotherapy Control and Elimination, 03*(01), 1–10. https://doi.org/10.4172/2090-2778.1000120
Erhonyota, C., Edo, G. I., & Onoharigho, F. O. (2022). Comparison of poison plate and agar well diffusion method determining the antifungal activity of protein fractions. *Acta Ecologica Sinica*. https://doi.org/10.1016/j.chnaes.2022.08.006
Farombi, E. O., & Owoeye, O. (2011). Antioxidative and chemopreventive properties of *Vernonia amygdalina* and garcinia biflavonoid. *International Journal of Environmental Research and Public Health, 8*(6), 2533–2555. https://doi.org/10.3390/ijerph8062533
Gadanya, A. M., Abubakar, M. Y., Maigari, F. U., Mudassir, L., & Abubakar, S. M. (2021). Comparative analysis of nutrients content and characterization of oil from two varieties of tiger nut (Cyperus esculentus). *Asian Journal of Research in Biochemistry*, 11–21. https://doi.org/10.9734/ajrb/2021/v8i130170
González-Palma, I., Escalona-Buendía, H. B., Ponce-Alquicira, E., Téllez-Téllez, M., Gupta, V. K., Díaz-Godínez, G., et al. (2016). Evaluation of the antioxidant activity of aqueous and methanol extracts of pleurotus ostreatus in different growth stages. *Frontiers in Microbiology, 7*. https://doi.org/10.3389/fmicb.2016.01099
Guo, N., Zhu, Y., Tian, D., Zhao, Y., Zhang, C., Mu, C., et al. (2022). Role of diet in stroke incidence: An umbrella review of meta-analyses of prospective observational studies. *BMC Medicine, 20*(1), 194. https://doi.org/10.1186/s12916-022-02381-6
Hassan, F., Edo, G. I., Nwosu, L. C., Jalloh, A. A., Onyibe, P. N., Itoje-akpokiniovo, L. O., et al. (2021). An inventory of medicinal plants used as sedative, analgesic and blood tonic in Abeokuta, Ogun State, Nigeria. *Acta Ecologica Sinica*. https://doi.org/10.1016/j.chnaes.2021.11.003
Howard, C., Johnson, W., Pervin, S., & Izevbigie, E. (2015). Recent perspectives on the anticancer properties of aqueous extracts of Nigerian *Vernonia amygdalina*. *Botanics: Targets and Therapy, 65*. https://doi.org/10.2147/BTAT.S62984
Hussain, S., Liufang, H., Shah, S. M., Ali, F., Khan, S. A., Shah, F. A., et al. (2022). Cytotoxic effects of extracts and isolated compounds from Ifloga spicata (forssk.) sch. bip against HepG-2 cancer cell line: Supported by ADMET analysis and molecular docking. *Frontiers in Pharmacology, 13*. https://doi.org/10.3389/fphar.2022.986456
Ighodaro, O. M., Adeosun, A. M., & Akinloye, O. A. (2017). Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. *Medicina, 53*(6), 365–374. https://doi.org/10.1016/j.medici.2018.02.001
Irondi, E., Agboola, S., Oboh, G., & Boligon, A. (2016). Inhibitory effect of leaves extracts of Ocimum basilicum and Ocimum gratissimum on two key enzymes involved in obesity and hypertension in vitro. *Journal of Intercultural Ethnopharmacology, 5*(4), 396. https://doi.org/10.5455/jice.20160814112756
Iruoghene Edo, G. (2022). Analysis of phytochemical constituents and antioxidant potential of bitter kola leaf extract towards bioactive food, nutrition and health resources. *Organic & Medicinal Chemistry International Journal*, (5), 11. https://doi.org/10.19080/OMCIJ.2022.11.555823
Iwo, M. I., Sjahlim, S. L., & Rahmawati, S. F. (2017). Effect of *Vernonia amygdalina* Del. leaf ethanolic extract on intoxicated male wistar rats liver. *Scientia Pharmaceutica, 85*(2), 16. https://doi.org/10.3390/scipharm85020016
Jan, R., Asaf, S., Numan, M., Lubna, & Kim, K. M. (2021). Plant secondary metabolite biosynthesis and transcriptional regulation in response to biotic and abiotic stress conditions. *Agronomy, 11*(5), 968. https://doi.org/10.3390/agronomy11050968
Jikah, A. N., & Edo, G. I. (2023). Moringa oleifera : A valuable insight into recent advances in medicinal uses and pharmacological activities. *Journal of the Science of Food and Agriculture*. https://doi.org/10.1002/jsfa.12892
Kumar, S., Yadav, A., Yadav, M., & Yadav, J. P. (2017). Effect of climate change on phytochemical diversity, total phenolic content and in vitro antioxidant activity of Aloe vera (L.) Burm.f. *BMC Research Notes, 10*(1), 60. https://doi.org/10.1186/s13104-017-2385-3
Kunnumakkara, A. B., Hegde, M., Parama, D., Girisa, S., Kumar, A., Daimary, U. D., et al. (2023). Role of turmeric and curcumin in prevention and treatment of chronic diseases: Lessons learned from clinical trials. *ACS Pharmacology & Translational Science, 6*(4), 447–518. https://doi.org/10.1021/acsptsci.2c00012
Larayetan, R., Ololade, Z. S., Ogunmola, O. O., & Ladokun, A. (2019). Phytochemical constituents, antioxidant, cytotoxicity, antimicrobial, antitrypanosomal, and antimalarial potentials of the crude extracts of callistemon citrinus. *Evidence-Based Complementary and Alternative Medicine, 2019*, 1–14. https://doi.org/10.1155/2019/5410923
Lisak Jakopović, K., Repajić, M., Rumora Samarin, I., Božanić, R., Blažić, M., & Barukčić Jurina, I. (2022). Fortification of cow milk with moringa oleifera extract: Influence on physicochemical characteristics, antioxidant capacity and mineral content of yoghurt. *Fermentation, 8*(10), 545. https://doi.org/10.3390/fermentation8100545
Maertens, A., Golden, E., & Hartung, T. (2021). Avoiding regrettable substitutions: Green toxicology for sustainable chemistry. *ACS Sustainable Chemistry & Engineering, 9*(23), 7749–7758. https://doi.org/10.1021/acssuschemeng.0c09435
Mainka, M., Czerwińska, M. E., Osińska, E., Ziaja, M., & Bazylko, A. (2021). Screening of antioxidative properties and inhibition of inflammation-linked enzymes by aqueous and ethanolic extracts of plants traditionally used in wound healing in Poland. *Antioxidants, 10*(5), 698. https://doi.org/10.3390/antiox10050698
Masyita, A., Sari, Mustika, Dwi Astuti, R., Yasir, A., Rahma Rumata, B., Emran, N., et al. (2022). Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. *Food Chemistry: X, 13*, Article 100217. https://doi.org/10.1016/j.fochx.2022.100217
McLennan, M. R., Hasegawa, H., Bardi, M., & Huffman, M. A. (2017). Gastrointestinal parasite infections and self-medication in wild chimpanzees surviving in degraded forest fragments within an agricultural landscape mosaic in Uganda. *PloS One, 12*(7), Article e0180431. https://doi.org/10.1371/journal.pone.0180431
Nwaoguikpe, N. R. (2010). The effect of aloe vera plant (aloe barbadensis) extracts on sickle cell blood (hbss). *African Journal of Food Science and Technology, 1*(3), 58–063.
Nwosu, L. C., Edo, G. I., & Özgör, E. (2022). The phytochemical, proximate, pharmacological, GC-MS analysis of Cyperus esculentus (Tiger nut): A fully validated approach in health, food and nutrition. *Food Bioscience, 46*, Article 101551. https://doi.org/10.1016/j.fbio.2022.101551
Olusola-Makinde, O., Olabanji, O. B., & Ibisanmi, T. A. (2021). Evaluation of the bioactive compounds of Vernonia amygdalina Delile extracts and their antibacterial potentials on water-related bacteria. *Bulletin of the National Research Centre, 45*(1), 191. https://doi.org/10.1186/s42269-021-00651-6
Onyibe, P. N., Edo, G. I., Nwosu, L. C., & Ozgor, E. (2021). Effects of vernonia amygdalina fractionate on glutathione reductase and glutathione-S-transferase on alloxan induced diabetes wistar rat. *Biocatalysis and Agricultural Biotechnology, 36*, Article 102118. https://doi.org/10.1016/j.bcab.2021.102118
Owheruo, J. O., Akpoghelie, P. O., Edo, G. I., Ojulari, A. E., & Agbo, J. J. (2023a). Proximate, mineral, sensorial and microbiological properties of chin-chin produced from okra seed and wheat flour blends. *Food Chemistry Advances, 2*, Article 100298. https://doi.org/10.1016/j.focha.2023.100298
Owheruo, J. O., Edo, G. I., Bashir, Z. A., Akpoghelie, P. O., & Agbo, J. J. (2023b). Quality evaluation of breakfast cereal meal produced from finger millet (Eleusine coracana) and roasted African yam beans (Sphenostylis stenocarpa) flour blends. *Food Science and Engineering*, 182–190. https://doi.org/10.37256/fse.4220232328
Owolabi, M. A., Jaja, S. I., Olatunji, O. J., Oyekanmi, O. O., & Adepoju, S. (2011). Attenuation of oxidative damage in alloxan induced diabetic rabbits following administration of the extract of the leaves of *Vernonia amygdalina*. *Free Radicals and Antioxidants, 1*(3), 94–101. https://doi.org/10.5530/ax.2011.3.13
Patel, D., Prasad, S., Kumar, R., & Hemalatha, S. (2012). An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pacific Journal of Tropical Biomedicine, 2*(4), 320–330. https://doi.org/10.1016/S2221-1691(12)60032-X
Perillo, B., Di Donato, M., Pezone, A., Di Zazzo, E., Giovannelli, P., Galasso, G., et al. (2020). ROS in cancer therapy: The bright side of the moon. *Experimental & Molecular Medicine, 52*(2), 192–203. https://doi.org/10.1038/s12276-020-0384-2
Phaniendra, A., Jestadi, D. B., & Periyasamy, L. (2015). Free radicals: Properties, sources, targets, and their implication in various diseases. *Indian Journal of Clinical Biochemistry, 30*(1), 11–26. https://doi.org/10.1007/s12291-014-0446-0
Rudrapal, M., Khairnar, S. J., Khan, J., Bin Dukhyil, A., Ansari, M. A., Alomary, M. N., et al. (2022). Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism(s) of action. *Frontiers in Pharmacology, 13*. https://doi.org/10.3389/fphar.2022.806470
Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., et al. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9th

edition. *Diabetes Research and Clinical Practice, 157*, Article 107843. https://doi.org/10.1016/j.diabres.2019.107843

Samje, M., Metuge, J., Mbah, J., Nguesson, B., & Cho-Ngwa, F. (2014). *In vitro* anti-onchocerca ochengi activities of extracts and chromatographic fractions of craterispermum laurinum and morinda lucida. *BMC Complementary and Alternative Medicine, 14*(1), 1–12. https://doi.org/10.1186/1472-6882-14-325

Semerdjieva, I. B., & Zheljazkov, V. D. (2019). Chemical constituents, biological properties, and uses of tribulus terrestris: A review. *Natural Product Communications*, (8), 14. https://doi.org/10.1177/1934578X19868394

Sharifi-Rad, J., Cruz-Martins, N., López-Jornet, P., Lopez, E. P.-F., Harun, N., Yeskaliyeva, B., et al. (2021). Natural coumarins: Exploring the pharmacological complexity and underlying molecular mechanisms. *Oxidative Medicine and Cellular Longevity, 2021*, 1–19. https://doi.org/10.1155/2021/6492346

Singh Makhaik, M., Shakya, K., & Kale, R. (2021). Dietary phytochemicals: As a natural source of antioxidants. *Antioxidants - Benefits, sources, mechanisms of action*. Intechopen. https://doi.org/10.5772/intechopen.99159

Sofowora, A., Ogunbodede, E., & Onayade, A. (2013). The role and place of medicinal plants in the strategies for disease prevention. *African Journal of Traditional, Complementary and Alternative Medicines*, (5), 10. https://doi.org/10.4314/ajtcam.v10i5.2

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249. https://doi.org/10.3322/caac.21660

Sweis, I. E., & Cressey, B. C. (2018). Potential role of the common food additive manufactured citric acid in eliciting significant inflammatory reactions contributing to serious disease states: A series of four case reports. *Toxicology Reports, 5*, 808–812. https://doi.org/10.1016/j.toxrep.2018.08.002

Thakkar, S., Anklam, E., Xu, A., Ulberth, F., Li, J., Li, B., et al. (2020). Regulatory landscape of dietary supplements and herbal medicines from a global perspective. *Regulatory Toxicology and Pharmacology, 114*, Article 104647. https://doi.org/10.1016/j.yrtph.2020.104647

Trendafilova, A., Moujir, L. M., Sousa, P. M. C., & Seca, A. M. L. (2020). Research advances on health effects of edible artemisia species and some sesquiterpene lactones constituents. *Foods, 10*(1), 65. https://doi.org/10.3390/foods10010065

Tungmunnithum, D., Thongboonyou, A., Pholboon, A., & Yangsabai, A. (2018). Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview. *Medicines, 5*(3), 93. https://doi.org/10.3390/medicines5030093

Ugbogu, E. A., Emmanuel, O., Dike, E. D., Agi, G. O., Ugbogu, O. C., Ibe, C., et al. (2021). The phytochemistry, ethnobotanical, and pharmacological potentials of the medicinal plant-*Vernonia amygdalina* L. (bitter Leaf). *Clinical Complementary Medicine and Pharmacology, 1*(1), Article 100006. https://doi.org/10.1016/j.ccmp.2021.100006

Usai, R., Majoni, S., & Rwere, F. (2022). Natural products for the treatment and management of diabetes mellitus in Zimbabwe-a review. *Frontiers in Pharmacology, 13*. https://doi.org/10.3389/fphar.2022.980819

Wang, J., & Wang, H. (2017). Oxidative stress in pancreatic beta cell regeneration. *Oxidative Medicine and Cellular Longevity, 2017*, 1–9. https://doi.org/10.1155/2017/1930261

Wong, F. C., Woo, C. C., Hsu, A., & Tan, B. K. H. (2013). The anti-cancer activities of *Vernonia amygdalina* extract in human breast cancer cell lines are mediated through caspase-dependent and p53-independent pathways. *PloS One, 8*(10), e78021. https://doi.org/10.1371/journal.pone.0078021

Zeli, C., Lombardo, M., Storz, M. A., Ottaviani, M., & Rizzo, G. (2022). Chocolate and cocoa-derived biomolecules for brain cognition during ageing. *Antioxidants, 11*(7), 1353. https://doi.org/10.3390/antiox11071353