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Review Article

Moringa oleifera: Recent Insights for Its Biochemical and Medicinal Applications

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Plants could be used for multiple medicinal purposes. *Moringa oleifera* (MO) is considered the most famous plant used for this purpose. The present review aimed to spot the light on the recent medicinal, biochemical, and nutritional applications of MO. The plant contains a huge number of nutrients such as fatty acids, amino acids, proteins, polysaccharides, minerals, and vitamins. It has been used to control glucose, lipids, proteins, minerals, vitamins, hormones, and antioxidants in many animals and human models. Its medicinal applications are also varied and wide; it could be used to control and manage lots of disorders. Extracts and isolated ingredients from the plant open the way for many researchers all over the world to study its biochemical and medicinal impact on many experimental and clinical models. The present review spots the light on the recent medicinal and biochemical significance of MO opening the discussion and demonstrating the strengths and weaknesses in the MO research area. Regardless of the contrary concept, we considered MO a promising plant that could be studied for its medicinal applications on both biochemical and molecular levels. We recommended further research on the molecular effects of MO in healthy and diseased models.

1. Introduction

1.1. History of Moringa oleifera. Medicinal plants and their extracts are widely used for multiple medicinal purposes all over the world [1–3]. Due to their huge extracts and bioactive ingredients, they could be utilized in the management, control, and treatment of many disorders [4–8]. A medicinal plant could be defined as any plant that contains bioactive ingredients used in therapy or contains a precursor for drug manufacture [9]. *Moringa oleifera* Lam. (MO) is a medicinal plant belonging to the *Moringaceae* family (Table 1). Its bioactive material is utilized in the treatment of a huge number of disorders with magical and amazing results to the extent that it is called a miracle tree [10]. Its bioactive components have antipyretic, antioxidant, anti-inflammatory, antiaging, antidiabetic, antihypertensive, immunomodulatory, hepatoprotective, and diuretic as shown in Table 2. Furthermore, recently, the plant has been approved to have antiparasitic activity [67], neuroprotective and cerebroprotective [68, 69], and antiproliferative activity against cancers [70]. On the other hand, the plant has a potential use in regenerative dentistry [71] and has the ability to control and attenuate osteoporosis [72]. Nowadays, its anticonstipation [73], anti-inflammatory [74], antioxidant [75], and neuroplasticity activities [76] have been confirmed. The plant is natively discovered in Indian forests and was consumed as a food additive [77]. The medicinal applications of MO were recorded in ancient medical books in many countries. In China, the first record of Moringa back to the bower script (volume II), about the 4^{th}–6^{th} century A.D. Thousands of years old, the medicinal purposes of Moringa plant parts have been recorded in the Ayurvedic Pharmacopoeia of India (API) [78]. The ancient Egyptians used Moringa oil as a sunscreen. Ancient Greeks discovered many medicinal applications for Moringa, and they introduced it to Romans where it spread everywhere in Europe while, in modern history in 1817, the Jamaican introduced Moringa oil for many food purposes till it reached to British Empire from where Moringa has been expanded all over the world [79]. Although the plant has great medicinal purposes, there is a need for further studies to elaborate and explore more details about its isolated compounds of synergistic action [80]. We and authors recommended further studies and advised us to continue research in this field.

1.2. Taxonomy, Synonyms, and Distribution. Moringaceae family is globally distributed especially in tropical areas. The plant is distributed in subtropical and tropical areas and includes about 13 species [81]. Globally, MO is widely distributed over Africa, Asia, Central America, and the Caribbean islands [82, 83]. MO in English is called the horseradish tree and drumstick tree; in Hindi, it is called Saijan; in Sanskrit, it is called Shigru [84]. The taxonomical classification and plant tree synonyms are illustrated in Tables 1 and 3 [85].

Table 1: Taxonomy of *Moringa oleifera*.

Plant kingdom	Plantae
Plant subkingdom	Tracheobionta
Plant super division	Spermatophyta
Plant division	Magnoliophyta
Plant class	Magnoliopsida
Plant subclass	Dilleniidae
Plant order	Capparales
Plant family	Moringceae
Plant genus	Moringa
Plant species	Oleifera

2. Bioactive Components and Their Medicinal Importance of *Moringa oleifera*

The tree of MO has many medicinal importance. It contains a huge number of bioactive compounds that could be used as it is or included in the formulation of drugs [86]. Organic agents such as protein, lipids, minerals, vitamins, tannin, flavonoids, saponins, phenolic acids, isothiocyanate, and others are active components isolated from MO illustrated in Figure 1. The pharmacological and medicinal aspects of these compounds are listed in Table 2. The cultivation processes and storage of plant parts have a great influence on the contents of these bioactive compounds which may affect its application and use [87].

3. Nutritional and Biochemical Significance of *Moringa oleifera*

3.1. Nutritional Significance of Moringa oleifera. A wide range of nutritinal components have been islated from MO seeds, roots, stems, leaves, flowers and pods as; proteins, carbohydrates, fats, glycosids and phenolic compounds [88]. These components are illustrated in Table 4. The plant parts contain a high amount of sulphur-containing amino acids, and they contain higher amounts of β-carotenes than carrots, higher amounts of L-ascorbate than oranges, higher levels of calcium than milk, higher potassium levels than that in bananas, nine times more iron than that in spinach, and four times more fiber than that in oats [110]. Other functional chemical groups have been extracted from leaves such as aldehydes, acids, amides, alcohols, phenols, vitamins, and phytosterols [111]. Due to their great nutritional properties, plant parts have been included in the formulation of both animal and human diets. Laboratory studies on the blood of models fed on MO investigated an increase in serum levels of calcium, proteins, phosphorus, and antioxidants but a decrease in glucose, triglycerides, and cholesterol levels [112].

3.1.1. Moringa oleifera as a Source for Animal Diets. Dietary preparations from MO were included in many animal diets such as chicken [113], fishes [114, 115], sheep [116], cows [117], and rabbits [118]. For chicken, Moringa diets formulated from leaves and stems improved the growth performance and carcass trait [119], and productivity and the quality of egg production [120]. MO extracts added to chicken diets lead to support and potentiate the immune response and introduce protection against infectious diseases [121]. MO diets are introduced to cows to improve colostrum quality, immunity, and milk production [117], protect the mammary epithelium from oxidants [122], and increase milk yield, rumen fermentation, and digestibility [123]. Diets supplemented with MO for pigs improved the reproduction performances, increased the protein contents of colostrum, and improved the antioxidant activities [124].

3.1.2. Moringa oleifera as a Source for Human Diets. MO has been also included in the formulation of human diets for many nutritional and medicinal purposes [125]. Moringa plant parts have been used as a natural agent for food fortification which is used to improve various aspects of food deficiencies, especially in children with micronutrient malnutrition [126]. It has been used to supplement humans with proteins and lipids of high biological values as well as a potent source for supplementation of iron, zinc, copper, and calcium [127]. It has been included in the diets of young women (teenagers) to improve their nutritional status and educational performance [128]. The addition of MO leaves powder to cookies or as an herbal drink improved the glycemic index, lowered blood glucose, improved appetite, and gastrointestinal health, and lowered both diastolic and systolic high pressure in highly consumed salt models [49, 129, 130]. MO dried leaves have been added to the

Table 2: Medicinal applications of *Moringa oleifera*.

Medicinal applications	Plant parts	Major findings	References
Analgesic	Roots	Inhibited the production of TNF-alpha and IL-2	[11]
Antiallergic	Pods and seeds	Inhibited beta-hexosaminidase, histamine, IL-4, and TNF-α release	[12]
Antiatherosclerotic	Leaves	Reduced cholesterol levels and reduced atherosclerotic plaque to 50% and 86%, respectively	[13]
Anticonstipation	Flowers and leaves	Adjusted stool number, weight and water contents of feces, and recovered the thickness of colon muscles and mucus	[14]
Antihelminthic	Seeds	Delayed the development of *Aedes aegypti larvae*, *Anopheles stephensi Liston*, and helminth eggs in irrigation water	[15–18]
Anti-inflammatory	Seeds, leaves, and roots	Downregulated TNF-α and interleukin-1β, and improved IL-6	[19–23]
Anticlastogenic	Leaves and pods	Decreased number of micronucleated peripheral reticulocytes	[24, 25]
Anticonvulsant	Leaves and roots	Enhanced the inhibitory mechanism through the release γ-amino butyric acid (GABA)	[26]
Antinociceptive	Leaves	Reduced the protein levels of ICAM-1 (intercellular adhesion molecule 1) and CD55	[27]
Antioxidant	Leaves and seeds	Included antioxidant agents such as vitamins, minerals, and phenols	[28]
Antipyretic	Leaves	Decreased body temperature	[29]
Antispasmodic	Leaves and seeds	Inhibited the release of acetylcholine	[30]
Antitumor	Seeds, leaves, and roots	Reduced the tumor weight and progression	[31]
Antiulcerogenic	Leaves and seeds	Increased the volume of gastric juice, PGE_2, IL-10, and GSH	[32–34]
Bactericidal	Leaves, stems, pods, and seeds	Showed antibacterial effect against *Staphylococcus aureus*, *Vibrio cholerae*, and *Escherichia coli*	[35–37]
Diuretic	Seeds	Increased urine output and increased urine volume and concentration	[30, 38]
Fungicide	Leaves, seeds, and roots	Showed antifungal activities against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum, and Microsporum canis*	[39, 40]
Hepatoprotective	Seeds and leaves	Enhanced plasma protein levels, reduced hepatic dysfunction markers, and regenerated hepatic tissue	[41–45]
Hypocholesterolemic	Leaves, seeds, and stem	Lowered plasma LDL cholesterol, VLDL cholesterol, and total cholesterol	[46–48]
Hypotensive	Seeds and pods	Decreased both systolic blood pressure (SBP) and diastolic blood pressure (DBP) and modulated angiotensin-1 converting enzyme (ACE) activity and expression	[49–54]
Immunomodulatory	Seeds, leaves, and flowers	Increased the proliferation of splenocytes, activated macrophages, increased NO production, and increased WBC counts and thymus weight	[55–61]
Potentiate memory	Leaves	Prevented memory impairment and errors	[62]
Radioprotective	Leaves	Prevented the electromagnetic and gamma radiation deleterious consequences	[63–66]

Table 3: Synonyms of *Moringa oleifera*.

Region	Name
Arabian	Rawag
Ayurvedic	Haritashaaka, Raktaka, and Akshiva
Chinese	La ken
English	Drumstick tree and Horseradish tree
French	Morungue
Gujarati	Suragavo
Hindi	Saguna and Sainjna
Latin	Moringa oleifera
Malayalam	Murinna and Sigru
Punjabi	Sainjna and Soanjna
Sanskrit	Subhanjana
Spanish	Angela, Ben, and Moringa
Tamil	Mulaga and Munaga
Unani	Sahajan

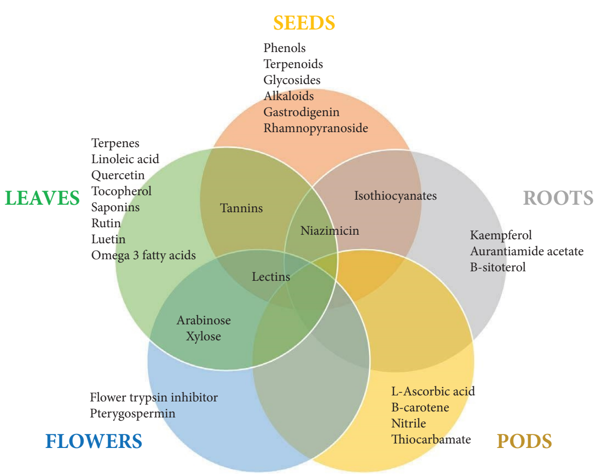

Figure 1: Bioactive compounds isolated from different plant parts of *Moringa oleifera*.

dishes and snacks of children to compete their malnutrition and deficiencies of β-carotenes or/and minerals and improve energy, iron, and zinc requirements [131–133]. In the same line, MO was effective to compete malnutrition in a clinical study performed on malnourished girls [134]. MO leaf powder could be added to cereals meals or sprinkled on infants' foods for improving micronutrient contents and competing vitamin A deficiency [135, 136]. Interestingly, Moringa was added to the diets of healthy overweight human models lead to improve the overweight and their lipid profiles [137].

3.2. Biochemical Significance of *Moringa oleifera*

3.2.1. *Moringa oleifera* and Glucose Status

(1) The Action of Moringa oleifera to Control Blood Glucose Level. MO were widely used to control blood glucose and its metabolism through multiple mechanisms (Figure 2). First, the plant extracts have been approved to inhibit many enzymes that could control glucose absorption or advanced glycation as intestinal α-glucosidase and pancreatic α-amylase [130, 138–140]. Another mechanism includes its ability to inhibit Na^+-dependent glucose uptake [141, 142]. The plant's high fiber led to a delay in gastric emptying [142]. Also, its contents of flavonoids and many phenolic compounds induce hypoglycemic action [143, 144]. The plants contain a huge amount of hypoglycemic bioactive agents such as catechin, cyanidin, ellagic acid, luteolin, kaempferol, quercetin, rosmarinic acid, and rutin [145]. The potential hypoglycemic power of MO has been approved in many clinical and laboratory studies for both animals and human diabetic models [146–149]. A majority of these studies' results showed a significant improvement in fasting blood glucose levels or glucose tolerance. The plant action revealed the normalization of the gene expressions of enzymes of insulin signaling, glycolytic mechanisms, glycogen storage, and decline in hepatic gluconeogenesis [150–152]. Aqueous extract of MO has been approved to increase the expression levels of glycogen synthase, hexokinase, and pyruvate kinase and lower pyruvate carboxylase expression in the liver of diabetic mice model [153] while seed extract activated glycogen synthase kinase-3beta (GSK-3β) [154]. The insulin-like proteins isolated from the MO plant contributed to the improvement of glucose uptake, and induced blood glucose reduction could be another way for its hypoglycemic action [155, 156]. MO stimulated insulin secretion through the activation of the insulin-dependent Akt pathway and increased GLUT-4 in skeletal muscle [157].

(2) Moringa oleifera as a Diabetic Control Plant. Some animal studies provided evidence for the potential use of MO as a hypoglycemic plant in diabetics and prediabetics [158]. While there is an existing viewpoint that these studies remain inconclusive and necessitate additional clarification and refinement [159]. Regarding human clinical studies, it is difficult to obtain scientific consensus about the antidiabetic action of MO as there are only few approvals with variable results [160]. The plant has been approved to improve blood glucose levels through its ability to increase insulin secretion sensitivity with a noticed inhibition of β-glucosidase and α-amylase activities and increases muscles and liver glucose uptake with noticed inhibition in intestinal uptake and decreases liver gluconeogenesis [161].

(3) The Hypoglycemic Evidences for Moringa oleifera. Prediabetics supplemented with MO showed an improvement in fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels [162], while, postprandial blood glucose levels (PBG) declined in diabetics [130], the same results obtained from studies on diabetic rats [163]. Fermented MO improved the glucose tolerance in obese mice [164]. MO leaves enhanced the insulin release, glucose uptake in the liver, and glycogen biosynthesis in alloxan-induced diabetic models [165]. In the same way, the leaf aqueous extract ameliorated the insulin resistance in mice [166]. Methanolic extract of MO leaves improved both glycogen synthesis and glucose tolerance in rats [151]. Moringa aqueous leaf extract showed a remarkable reduction in blood glucose concentration in rats [167]. Systemic and topical applications of MO leaf aqueous extract positively improved wound healing in

Table 4: Nutritional significance of *Moringa oleifera*.

Nutritional contents	Members	References
Amino acids	Leucine, aspartate, glutamate, and proline	[89]
Glycosides	Sitogluside	[90]
Minerals	Zinc, iron, potassium, calcium, selenium and phosphorus	[91, 92]
Peptides	LALPVYN, LHIAALVFQ, FHEEDDAKLF, hevein-like peptide FLSeML, LSeMAAL, LASeMMVL, SeMLLAA, LSeMAL, and antimicrobial peptide	[93–96]
Phenolic compounds	Quercetin, phenolic acid, tannins, and saponins	[97–99]
Carbohydrates	Glucosinolate and polysaccharides	[60, 100–102]
Proteins	Protease and amylase	[103, 104]
Vitamins	Pyridoxine, vitamin E, niacin, and ascorbic acid	[89, 105, 106]
Fatty acids	Octadecanoic acids, palmitic acid, and omega-3 fatty acids	[92, 107]
Flavonoids	Flavones, anthocyanins, myricetin, and kaempferol	[99, 108, 109]

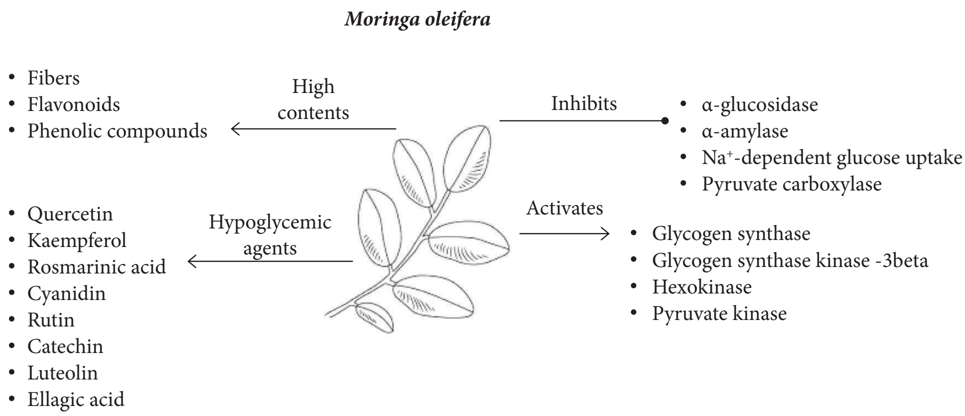

Figure 2: The hypoglycemic action of *Moringa oleifera*.

diabetic rats [168]. MO enhanced the regulation of circulating glucose through the regulation of Hsp70 and ILP2 (insulin-like peptide 2) [169] and enhanced the uptake of glucose in adipocytes [170]. It has been approved that the flavonoids and polysaccharides isolated from MO leaves had synergistic action to delay glucose diffusion, dialysis, and delaying starch digestion [171]. In the same line, MO polysaccharides improved glucose levels and metabolism in diabetic models [172]. The supplementation of leaves and seeds potentially activated monoamine oxidase (MAO), adenosine triphosphatase (ATPase), adenosine deaminase (ADA), acetylcholinesterase (AChE), arginase, lactate dehydrogenase (LDH), and angiotensin-I converting enzyme (ACE) activities in diabetics [173]. Leaves potentially control both insulin levels and blood glucose levels in rats with polycystic ovaries [144].

3.2.2. Moringa oleifera and Lipids. The potential role of MO extracts in lipids metabolism has been illustrated in Figure 3. It has been approved that MO supplementation leads to an improvement in the metabolic status of obese mice [89, 174]. Moreover, it controlled hypertriglyceridemia and hypercholesterolemia in rodent models [175]. Its fermented leaf extracts have the ability to decrease hepatic accumulation of lipids in obese mice [164], and it alleviated the metabolic syndrome in rats inducing an improvement in lipid profile and adipokines such as adiponectin and leptin [176]. Furthermore, rats that received MO leaf extract showed great resistance against consequences resulting from metabolic syndrome induced by high fructose and fat diets [177]. The leaves reduced lipids absorption in obese rats [42]. Leaf extract lowered levels of TC, HDL-C, LDL-C, and TAGs through an invitro inhibition of pancreatic lipase and α-glucosidase [178]. The same results were obtained when MO was added to ice cream introduced to rats [179]. In adipocytes, MO has the ability to increase glucose uptake, promote lipolysis, and attenuate adipogenesis by controlling the cell cycle genes [170, 180].

Seed oil extracts reduced leptin and resistin indicating antiobesity activity [181]. Serum examinations indicated that dietary polysaccharides extracted from MO leaves reduced TC, TAGs, and LDL-C in rabbits stressed with heat and modulated their lipid metabolism [182]. Similarly, the administration of MO polysaccharides to mice induced protection against high-fat diet-induced obesity [183]. MO prevented the progression of liver damage and inhibited de novo lipogenesis in the liver [184]. In a similar study, it protected liver damage in ethanol-induced liver damage and reduced TAG levels in mice [185]. Seed extracts upregulated the AMPK and PPARα and downregulated mTOR and SREBP-1 [44]. Moringa also downregulated the expression of PPARγ, C/EBPα, and FAS and upregulated the expression and phosphorylation of ACCl and AMPKα [186].

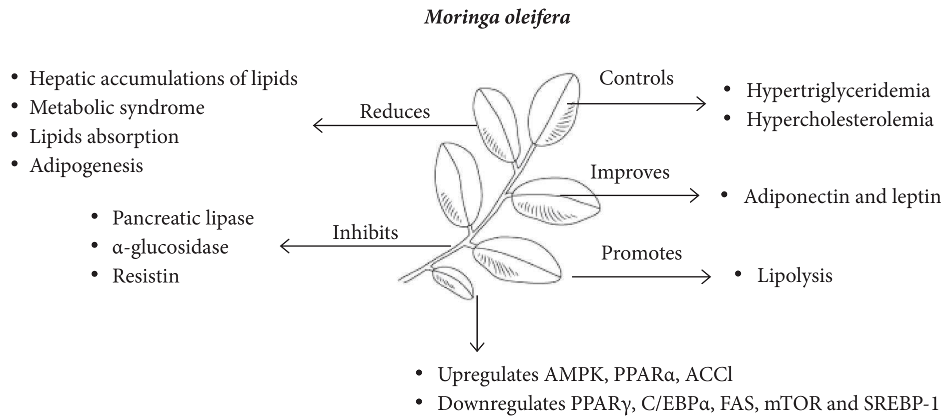

Figure 3: The biochemical action of *Moringa oleifera* on lipids.

3.2.3. *Moringa oleifera and Proteins*

(1) Proteins and Enzymes from Moringa oleifera. Qualitative analysis of plant parts indicated the presence of many important proteins and enzymes which are included in the synthesis of vitamins, iron transporters, and calcium storage proteins [187]. MO provides proteins for people of low income in consequence, and the plant has been expected to help to reduce kwashiorkor symptoms and its related consequences [188]. The studies approved also that the plant parts could be an alternative resource of proteins used for the preparation of animal diets [189]. It has been approved that MO supplementation enhanced animal reproduction and elevated the protein contents in their milk [124]. Seed oil extracts regulated and enhanced plasma proteins, and reduced the hepatic and renal as well as inflammatory parameters in rats [41]. Polysaccharides isolated from MO also upregulated the expression of enzymes included in protein digestion and absorption in rabbits [118]. Recently, many isolated proteins from MO leaves could improve protein digestibility [190, 191]. In the same way, cysteine peptidase derived from MO seeds is considered a promising alternative to rennet [192]. Milk-clotting peptidase and protease have been isolated and purified from MO seeds and could be used in the dairy industry due to their thermostability [193]. Bioactive compounds like quercetin could target many proteins of high biological functions like p53. Isolated compounds showed great binding affinity to p53 in a molecular docking model the matter which opens the window to apply MO as an active agent in cancer research [194]. Coagulant protein isolated from MO possessed a great antimicrobial action against many isolates of bacteria isolated from water [195]. Leaf extract could modulate the differentiation of brown adipose tissue through the upregulation of bone morphogenetic protein 7 (BMP7) levels in obese mice [196]. The ethanolic extracts were associated with significant normalization of proteins of antioxidant, anti-inflammatory, and antiapoptotic activities [197]. Mass spectrometric results revealed that there was a modulation in the expression of about 125 proteins included in metabolism, signal transduction, transcription, and translation in models supplemented with pods [198]. MO extracts also have been shown to introduce protection against apoptosis and oxidative stress induced in human neuroblastoma cells through their ability to activate caspase-3 [199]. Leaf extracts protected cells from peroxidative damage and stimulated osteogenic induction in stem cells through the activation of phosphatidylinositol 3-kinase (PI3K/Akt/Foxo1 pathway [200]). MO decreased the inflammatory cytokines as IL-6, IL-1β, TNF-α, and IFN-β, inhibited the nuclear transfer and expression of the cellular protein transcription factor EB (TFEB), and declined the cellular autophagy [201]. Leaves extracts also alleviated inflammation in colorectal cancer models through the downregulation of TNF-α, IL-2, and IL-6 [202]. Polysaccharides extracted from MO-elevated total proteins and increased protease and amylase activities in early pregnant goats [203]. MO extracts given to laying hens lead to an increase in total proteins and albumin and reduced urea [204]. MO polysaccharides significantly improved the plasma proteins and enhanced protease and amylase activities in goats [103]. MO increased the expression of vascular endothelial growth factor (VEGF) and transforming growth factor beta-1 (TGF-β1) leading to the contraction of wounds, reduction of epithelization time, increasing antioxidant activities, and reduction of capillary density [205].

(2) Peptides and Peptide Fractions of Moringa oleifera. Many peptides isolated from MO are illustrated in Table 5. Furthermore, hydrolysis of MO seeds globulin with trypsin produced many peptides that have potential antioxidant and antihypertensive action [214]. Peptides of hypotensive effect were isolated from MO as angiotensin-converting enzyme (ACE), Gly-Leu-Phe-Phe (GLFF), and renin peptides Leu-Gly-Phe-Phe (LGF) [51]. Many peptides of antimicrobial agents have been purified from MO proteins [215]. Another peptide (<7.5 kDa) has been isolated from MO and possessed an efficient antimicrobial activity [216]. An antimicrobial peptide (AMP) has been also, isolated from MO seeds with an inhibitory action against S. aureus through inhibition of DNA gyrase and dihydrofolate reductase [96]. Another peptide of hypoglycemic action has been isolated

from MO and interacted with α-glucosidase through hydrogen bonding and hydrophobic interactions [217].

(3) Moringa oleifera, Uric Acid, Urea, and Creatinine. Many studies shed light on the potential influence of MO extracts on protein metabolites such as urea, uric acid, and creatinine. Methanolic extracts of MO decreased both BUN and creatinine in renal ischemic rats' models [218]. Leaves supplementation reduced both serum uric acid and creatinine [219], ameliorated serum uric acid levels [220], improved the hematological indices, and reduced uric acid levels in stressed models [221] in consequence, and MO returned the uric acid to its normal level in diabetic rats and mice [222, 223]. Also, MO seeds reduced the uric acid level in the blood of diabetic rats [224] providing evidence of the hypouricemic power of leaf extracts [225].

3.2.4. Moringa oleifera and Minerals. MO is characterized by its huge content of many macro and microelements. Its seeds are rich in iron (Fe), zinc (Zn), phosphorus (P), magnesium (Mg), copper (Cu), and manganese (Mn) [226] while its leaves are full of calcium (Ca), potassium (K), sulphur (S), and Fe [92, 227, 228]. Selenium (Se) and iodide (I) are also present in high concentrations in many parts of edible plants [229]. Its richness of minerals made it a great nutritional supportive plant of high biological value and could be used in the control, management, and treatment of micronutrient malnutrition in both humans and animals, help in bone growth and strength, and competing anemia [126, 134, 188, 230–232].

(1) Moringa oleifera and Calcium. MO is approved to contain higher Ca than milk and more potassium (K) than that in bananas [110, 233]. Many methods could be used for the formulation and extraction of MO to increase its bioaccessibility and bioavailability of Ca [234]. Ca contents of leaf extract promoted the growth and development of rats exposed to Ca deficiency, stimulated deposition of Ca in bones, promoted bone growth and strength, and declined resorption of bone [188, 235]. MO has been demonstrated to modulate the Ca signals in tissues, the matter that approved its hypotensive action [236]. Its extracts also were approved to block the entrance and mobilization of Ca^{+2} in sarcolemma [237]. Recently, the plant extracts were used to modify the amorphous/crystallization status of Ca and P the matter which opens the way for its use in drug delivery and nutraceutical applications [238]. Additionally, MO regulates the Ca levels in mitochondria enabling its ability to prevent mitochondrial dysfunction increasing the potentiality of mitochondrial membranes [105].

(2) Moringa oleifera, Iron, and Zinc. On a wide scale, MO has been added to formulate diets to compete anemia and bone problems due to its high content of Fe included in its leaves [239]. It is incorporated into the diets of children, pregnant, and lactating women to overcome iron deficiency and malnutrition [227, 240]. Leaves powder has been used as a fortified food for iron supplementation and to increase its bioaccessibility [241]. The addition of lime juice, ascorbic acid, and citric acid to MO-fortified diets increased iron and zinc bioavailability and bioaccessibility [242]. Fermented leaves also could be another way to increase Fe bioavailability in MO enabling its use to control anemia in children [243]. There are many forms to add MO for animal and human diets; MO leaf flour as a source of Fe and Zn could be added to biscuits to improve pregnant mothers' health who have anemia [244]. For potentiation of children's health and protecting them from the consequences and development of anemia, MO leaf powders have been added to their formulated diets. There is a proportional relationship between the time of using MO in diets and reduction of anemia among children [132, 245].

3.2.5. Moringa oleifera and Vitamins. β-Carotenes, α-tocopherols, and L-ascorbic acid, along with vitamins B1, B2, and B3, were identified in many plant parts of MO especially leaves [85, 246–248]. The amount of vitamin A in MO is greater than that in carrots, and the amount of L-ascorbic acid is greater than that in orange [110]. It has been approved also that the recommended daily allowance of vitamins A and C could be covered by the daily use of Moringa seeds and leaves [243, 249]. Clinical studies also approved the ability of MO to improve vitamin A (retinol) kinetics and store with an ameliorated malnutrition status in children [250, 251], improvement of vitamin A levels in postmenopausal women [252], and improved the serum retinol levels in adolescent girls. [253].

3.2.6. Moringa oleifera and Hormones

(1) Moringa oleifera and Reproductive Hormones. Many biochemical studies have demonstrated the possible effect of MO on both males and females. Its effect tended to be dose-dependent. In females, MO reduced serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estrogen while in males, there was an increase in serum concentration of FSH, LH, and testosterone [197, 254–256]. This illustrated its effect on male fertility, enhancement of semen quality, and sex hormones. Therefore, MO is more beneficial for male reproduction than that for female reproduction [256–258]. Furthermore, MO extracts improved male fertility through elevation of serum testosterone and gonadotrophin levels in obese rats [259], improved sperm functions, decreased FSH and increased inhibin B levels in mice [260], and normalized the level of testosterone in rats [261]. For its androgenic effect on testosterone chemistry and reserve, MO leaf extracts have been reported to inhibit β-hydroxylation of testosterone by cytochrome P450 3A4 (CYP3A4) [262], increased the testosterone productivity in Leydig TM3 cells [263], and reduced the level of testosterone in prostatic hyperplastic rats [264]. The combination of MO leaves with nanoparticles like zinc oxide nanoparticles

Table 5: Medicinal significances of bioactive components in different parts of *Moringa oleifera*.

Plant parts	Bioactive components	Medicinal significances	References
Leaves	Vitamins (A, C, E, and B complexes)	Immunomodulation, antioxidants, vision, energy, and metabolic disorders	[87, 206, 207]
	Minerals (Ca, K, Fe, Mg)	Bone ossification and regulation of blood pressure	
	Flavonoids (quercetin)	Hypoglycemic, antioxidants, anticancer, and hypotensive properties	
	Isothiocyanates	Anticancer and anti-inflammatory properties	
	Fatty acids	Omega-3 fatty acids lowering cholesterol	
	Polyphenols (rutin and lutein)	Hypoglycemic and hypolipidemic properties	
Flowers	Phenols	Hypoglycemic and antioxidant properties	[87, 207, 208]
	Flavonoids	Antioxidants, hypoglycemic anticancer, and hypotensive	
	Alkaloids	Anticancer	
	Essential oils	Antimicrobial properties	
	Beta-carotenes	Vision, skin health, and immune functions	
Seeds	Oleic acid	Cardiovascular health	[87, 99, 207, 209]
	Polyphenols	Antioxidants properties	
	Phytosterols	Cholesterol-lowering activities	
	Glycosides	Anticancer properties	
	Benzyl isothiocyanate	Anti-inflammatory properties	
Roots	Alkaloids	Diverse biological activities (anticancer and anti-inflammatory properties)	[87, 207]
	Flavonoids	Antioxidants, anticancer, and hypoglycemic properties	
	Isothiocyanates	Anticancer, antioxidant, and anti-inflammatory properties	
	Phytosterols	Cholesterol-lowering activities	
Pods	Vitamins (A and C)	Antioxidants, vision, and energy metabolism	[50, 87, 207, 210–213]
	Minerals (Ca, Fe, K, and Mg)	Bone ossification, blood pressure regulation, and antianemia	
	Flavonoids	Antioxidant, antimicrobial, and hypoglycemic properties	
	Fibers	Digestive health and regulation of blood sugar levels	
	Phytosterols	Cholesterol-lowering activities	
	Isothiocyanates	Anticancer, antioxidants, and anti-inflammatory and hypotensive properties	
	Polyphenols	Antimicrobial, anti-inflammatory, hypoglycemic, and chemopreventive properties	

(ZnONPs) could potentiate the biogenic synthesis of LH, FSH, and testosterone through the regulation of the hypothalamus-pituitary-testicular axis [265]. Contrary to the previously mentioned, MO seed extracts have been reported to potentiate male reproductive toxicity as they decreased testosterone, LH, sperm motility, and sperm in rats [266].

(2) Moringa oleifera and Thyroid Hormones. In related to its effect on thyroid hormones, MO induced a significant decline in serum levels of thyroid-stimulating hormone (TSH) and an elevation in T3 and T4 in patients with primary hypothyroidism [267]. Furthermore, it inhibited the peripheral conversion of T4 to T3 illustrating its potent role in conserving T4. It should be noted that this inhibitory effect was significant in females than in males [268, 269]. On the contrary, the consumption of Moringa more than twice a day may be associated with the induction of goiter in human [270].

(3) Moringa oleifera and Metabolic Hormones. It has been recorded that the MO has a direct effect on β-cells of the pancreas, stimulating insulin secretion [144, 157]. Clinically, high doses of leaf powder in the form of capsules induced a considerable increase in insulin secretion in healthy populations suggesting its role as an agent in the controlling of blood glucose [146]. Invitro studies approved its influence on direct and/or indirect increases in insulin signaling and sensitivity [152]. Accordingly, it provided a protection against the consequences of insulin resistance, hyperinsulinemia, increased low-density lipoprotein (LDL), increased visceral fat, and high liver weight [177]. The isolated agents from MO opened the window for innovative formulation of drugs against diabetes mellitus [148]. On the other hand, MO leaves have been recorded to elevate the plasma insulin such as growth factor I (IGF-I) [271] insulin [144] and leptin hormones [42, 184] leading to inhibiting adipogenesis [180, 272]. On the contrary, others recorded its ability to reduce serum leptin [152, 181, 273, 274] leading to an increase in the energy expenditure and controlling obesity [275].

(4) Moringa oleifera, Prolactin, and Progesterone. Phytohormones such as auxins, cytokinins, and gibberellins have been approved to be contained in significant amounts in MO leaf extracts [276]. Due to the presence of these phytohormones, consumption of MO during pregnancy may be unuseful as the plant could change the hormonal profile of pregnant women. Phytochemical contents and their metabolites may induce uterine contractility leading to abortion, affecting the conception rate, inducing teratogenicity, and producing congenital anomalies [277]. Regardless of its harmful use during pregnancy, the plant could be used as a galactagogue increasing milk letdown in lactating females and improving milk volume and infant weight better than other pharmacological galactagogues [278]. A strange point here has been reported; MO could be used to initiate and establish lactation even in nongestational women [279]. Its leaf extract has been recorded to resist the negative effect of stress on hormonal balance during pregnancy [280] while consumption of seed extract induced a decrease in serum progesterone in heat-stressed females [281].

(5) Moringa oleifera, Serotonin (5-Hydroxytryptamine), and Melatonin. It has been recorded that the brain level of serotonin is elevated in aged rats administered aqueous extract of MO [282] while the aqueous extract from its roots significantly elevated the serotonin levels in the cerebral cortex, cerebellum, midbrain, and caudate nucleus [283]. Serotonin release also has been potentiated through the effect of MO 5-hydroxytryptamine 3 (5-HT3) receptors in experimental ulcer models [284]. The MO seed extract was able to ameliorate the level of serotonin in the cerebellum of titanium oxide nanoparticles induced damaged brain in rats [285]. In depressed rats, it increased serotonin release through the noradrenergic-serotonergic neurotransmission pathway [286] and recovered the serotonin levels in rats affected with Alzheimer's disease [287]. It has a protective effect against gastric ulceration through increasing 5-HT levels and enterochromaffin cell count [288]. It also potentiated the sleep time induced by pentobarbitone and increased serotonin levels in rats [289]. Up to this moment, there were no studies on the effect of MO on melatonin levels in experimental animals or humans. As well as, phytochemical studies revealed the absence of melatonin in MO extracts [290].

3.2.7. Moringa oleifera and Antioxidants. The ingredients isolated from many plant parts such as leaves, seeds, or buds have been examined for their antioxidant power in many animals' models. Plant extracts have been reported to elevate antioxidant enzyme activities and decrease hydroperoxides (HP) and thiobarbituric acid reactive substances (TBARS) [291].

(1) Antioxidant Bioactive Ingredients form Moringa oleifera. Active ingredients such as niazirin and isothiocyanate have been isolated form MO and have been approved for their potent antioxidant activity and could be used to control many oxidant-related stresses [292, 293], while its polysaccharides significantly lead to enhancement of CAT, SOD, and GPx activities and declined malondialdehyde (MDA) and reactive oxygen species (ROS) levels [294]. MO supplementation enhanced the activity of SOD, CAT, GPx, and lower MDA [124, 295]. MO also could compete with the heat stress in birds through its power to modulate the antioxidant system in heat-stressed broilers. The birds fed on MO showed better antioxidant profiles and low lipid peroxide markers [113]. The leaf extract of MO has been approved also to increase TAC and improve tolerance of immunity [154, 166]. Notably, leaf extract also showed an ability to strength the intracellular antioxidant defense system (SOD, CAT, and GSH) and lowered MDA in many experimental models [296]. Leaf extracts of MO could be also used to improve the health of muscles through its ability to influence the redox state in myotubes against hydrogen peroxide oxidant stresses. It elevated the activity of thioredoxin (Trx), SOD, CAT, GPx, and GST. It also mitigated lipids and protein peroxidation by lowering the levels of TBARS and protein carbonyls [297]. The methanolic extract of MO

improved the semen quality in rams through its ability to lower the MDA and elevate SOD, GPx, and ascorbic acid in ram frozen semen [298]. Interestingly, supplementation of MO could protect gastric mucosa in ulcerated stomach by increasing the activities of CAT, SOD, and GPx in rats' stomach [33]. In the same prospect, alcoholic extract from MO has been approved to protect the stomach from ulcers induced by bisphenol via its antioxidant activities [32]. Leaves extracts have been approved to improve ulcerative colitis pathological consequences through their antioxidant power, and they elevated CAT and SOD and lowered MDA in rat's serum [299].

(2) Antioxidant Power of Moringa oleifera at Molecular Level. At molecular levels, MO tended to reduce the oxidative stress via activation of a basic leucine zipper transcription factor that links to the promoter domain of the antioxidant response element (Nrf2-ARE) signaling, elevating the expression of Nrf2 target genes and declining the expression of transforming growth factor beta-1 (TGF-β1) signaling [300]. It has been also approved to stimulate the total antioxidant capacity through the suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) translocation, upregulation of the Kelch-like ECH-associated protein 1- (Keap1-) nuclear factor-erythroid 2-related factor 2 (Nrf2) (Nrf2/Keap1) system, reducing the activation of protein kinase C, zeta (PKCζ), and inhibiting the NADPH oxidase 4 (Nox4) protein expression [301].

4. Conclusion

Due to its huge content of bioactive compounds and ingredients, *Moringa oleifera* has been approved for its medicinal and nutritional value. Further studies are recommended to discover more promising active compounds with therapeutic and synergistic effects for chronic and serious disorders. Furthermore, the molecular effect of MO should be studied on a wide range to explore more molecular mechanisms for understanding its role as a medicinal plant.

Data Availability

The data that support the concept of this review will be available from the corresponding author upon a reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All the authors conceptualized the study, provided software, validated the study, provided resources, wrote the original draft, reviewed and edited the manuscript, and visualized the study.

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