WISELEAF SCIENTIFIC VENTURES

Moringa oleifera (*Moringaceae*): A Miracle Tree in Pharmacognosy

Chapter 7

Safety, Toxicity and Standardization of *Moringa oleifera*

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Abstract

The nutritional profile and various pharmacological activities of Moringa oleifera have made it a plant of great interest in recent years, making it one of the most studied in modern pharmacognosy. Although it is widely used in traditional and commerce, scientific assessment of its safety, toxicity, and standardization is still needed to guarantee its therapeutic efficacy, quality control, and regulatory approval. The present chapter critically examines the toxicological profile and standardization procedures of Moringa oleifera in the present-day research of herbs. The chapter emphasizes on the acute, subacute, chronic, reproductive and genotoxicity studies performed with various plant parts such as leaves, seeds, bark and roots. Dose-dependent toxicity, phytochemical variation, anti-nutritional factors and potential herb–drug interactions that could affect clinical safety are emphasized. Additionally, the chapter reviews effect of culture conditions, geographical variation, harvesting and extraction methods on the phytochemical uniformity and biological activity of Moringa oleifera preparations. The standardization section is based on the recent quality control parameters used in pharmacognostic and phytopharmaceutical assessment such as macroscopic and microscopic characterization, physicochemical analysis, chromatographic fingerprinting, quantification using markers, microbial limit tests, and stability studies. The advanced analytical techniques employed for authentication and quality assessment, like HPLC, GC–MS, TLC are also discussed. The chapter also presents the current regulatory views and international guidelines towards herbal standardization and safety evaluation. In summary, this chapter offers a scientific review of the toxicological aspects and quality control of Moringa oleifera for safe therapeutic use and commercialization in the healthcare and pharmaceutical sector.

Keywords: Moringa oleifera, Herbal standardization, Toxicological evaluation, Quality control analysis, Phytopharmaceutical standardization

1. Introduction

Moringa oleifera commonly known as the drumstick tree, horseradish tree or miracle tree is one of the most studied medicinal plants, because of its remarkable nutritional profile and pharmacological activities. It belongs to the family Moringaceae which comprises of thirteen species, occurring in the tropical and subtropical regions of the world. Although M. oleifera is native in the Indian subcontinent, including India, Pakistan, Bangladesh and Afghanistan, it is well adapted to drought and soils, so it is grown in other parts of Asia, Africa, Latin America and parts of the Middle East.[1]It is fast growing plant, high biomass production and it is available throughout the year making it more and more important in the food, pharmaceutical, cosmetic and nutraceutical industries worldwide.Nearly all of the parts of the plant are therapeutic. Traditionally leaves, flowers and immature pods, seeds and oil extracted from seeds, bark and root have been used for nutrition supplementation and in the treatment of various ailments. Among these, leaves have received scientific attention, because of their highly nutritive

composition. They are rich in proteins, essential amino acids, vitamins and minerals, dietary fibers and various bioactive phytochemicals.[2]The leaves are a good source of vitamins A, C and E, calcium, potassium, magnesium, iron and polyunsaturated fatty acids and thus serve as a nutritional supplement for malnutrition and micronutrient deficiencies.The high content of phytochemicals makes M. oleifera a potential source of pharmacological activities. Secondary metabolites can be divided into various classes such as flavonoids, phenolic acids, glucosinolates, isothiocyanate, alkaloids, tannins, saponins, terpenoids and thiocarbamates. All the bioactive markers discussed above, namely, quercetin, kaempferol, rutin, chlorogenic acid, niazimicin and glucomoringin are likely to be the leading compounds behind its plethora of biological activities. The compounds have been found to possess strong antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, hepatoprotective, cardioprotective and neuroprotective properties.In recent years, M. oleifera has been a topic of great interest as a crop for functional foods, dietary supplements, beverages, dairy alternatives and cosmetics.[1,2] The huge demand of consumers to natural products and plant-based therapeutics has also further stimulated the commercialization all over the world of moringa derived products. But some International Organization such as United States Food and Drug Administration (FDA), Cosmetic Ingredients Database (CosIng) and European Food Safety Authority (EFSA) have observed the potential of some moringa formulations for food and cosmetic industry applications.Although it has a great therapeutic potential, there are some scientific issues that haven't been addressed yet. Leaf preparations are usually considered safe, but the alkaloidal constituents of the other parts of the plant are believed to be reproductive toxic and abortive.[3]Moreover, since antinutrient compounds such as phytates, oxalates, tannins and saponins may inhibit the absorption of minerals when consumed in excess, it is important to consume these seeds in moderation. These are problems that will alert the need to do toxicology testing before using them on a large scale as a therapy.Therefore, it is very important to develop toxicological profile and standardisation protocol of this plant which is scientifically validated to translate the traditional use towards evidence based therapeutic applications.[3,4] The chapter critically reviews the therapeutic importance, safety concerns, standardization strategies, problems and future prospects for its pharmaceutical and nutraceutical uses.

2. Therapeutic potential of Moringa oleifera

Moringa oleifera is a plant with a variety of biological activities which have attracted considerable attention for its therapeutic potential. The coordinated action of a huge number of phytoconstituents allow the plant to affect multiple pathological pathways simultaneously and makes it an excellent whole system health care solution.[4] Antioxidant activity is one of the many properties that has been most studied in M. oleifera. Oxidative stress is a key factor in the pathogenesis of various chronic diseases, such as cardiovascular diseases, diabetes mellitus, neurodegenerative diseases and cancer.[4,5] Moringa leaves are rich in flavonoids, phenolic acids,

carotenoids and vitamin C which are effective in scavenging the reactive oxygen species and have an inhibitory effect on lipid peroxidation. Quercetin and chlorogenic acid are especially interesting in this respect for their ability to form free radicals and to prevent free radicals from reacting with cellular macromolecules.[5] Several studies have demonstrated that the supplementation of moringa can lead to significant increase in the concentrations of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase which are naturally occurring in the body.Another crucial therapeutic property of M. oleifera is its anti-inflammatory property. Many metabolic and degenerative diseases are associated with chronic inflammation. Experimental studies have proven that moringa extracts are able to inhibit inflammatory mediators by regulation of the nuclear factor-kappa B (NF-κB) pathway and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. These mechanisms decrease the synthesis of pro-inflammatory cytokines such as tumour necrosis factor alpha, interleukin-1 beta and interleukin-6. In such a manner, moringa could play a significant part on the treatment of inflammatory diseases.[6]So many hepatoprotective effects have been also reported. Liver is a target organ of oxidative damage by xenobiotics and environmental toxins. Antihepatic effects of moringa leaf extracts have been shown to be protective against chemically-induced liver injury by significantly decreasing the serum level of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase. Moreover, moringa inhibits the accumulation of lipids and expression of inflammatory genes in liver tissues. It is believed that this is due to the abundance of flavonoids that it contains.[5,6]Moringa also has shown potential antidiabetic and cardiometabolic properties. There have been a number of experimental studies demonstrating beneficial effects of supplementation on insulin sensitivity, glucose metabolism and lipid profile. The chlorogenic acid delays the assimilation of glucose and the quercetin stimulates the insulin secretion and the peripheral utilization of glucose. At the same time, moringa decreases the risk of cardiovascular diseases by decreasing the total cholesterol, triglycerides and low-density lipoproteins (LDL) and by increasing high-density lipoproteins (HDL).[7]Moreover, the plant also aids in the healing of wounds and repairing of tissues. Incorporation of hydroalcoholic leaf extracts in biomaterials (chitosan gels) has been recently shown to have a faster wound contraction, collagen production and epithelialization. The effects are beneficial in the post-surgical healing procedure and in scar reduction. Based on these results it is suggested that it can be used in skin care and cosmetic products.All these pharmacological activities point towards the high therapeutic value of M. oleifera.[8] Despite these positive experimental results, however, more well-designed clinical trials are needed to confirm these results and to determine the optimal dosage for long-term therapeutic use.

3. Toxicological profile of *Moringa oleifera*

The use of Moringa oleifera in pharmaceuticals and nutraceuticals or functional foods has gained popularity and so a full toxicological profile is needed to enable its safe use in

therapeutic applications. The plant is used traditionally and is generally considered safe for use; however, due to various phytochemical composition and toxicity of different parts of the plant it is necessary to validate the plant through preclinical and clinical studies.[9]Current evidence suggests that there is a favorable safety margin with leaf preparations but with root, bark and some seed preparations, care should be exercised due to their potential toxic effects.The traditional safety evidence is the first understanding of the toxicological behaviour of M. oleifera. The leaves and immature pods of moringa have been used in Asia, Africa and Latin America for centuries with no reports of serious adverse health effects.[10] Leaves have been extensively utilized for the treatment of malnutrition, gastrointestinal disease and infection and inflammation. A lot of empirical evidence is generated to substantiate their general safety of use. But, there is a traditional knowledge that excessive consumption of root and bark preparations should be avoided, indicating that there might be harmful compounds present in the mentioned parts of the plants. Since then, this has been confirmed by scientific research.[11]Acute toxicity testing of the leaf extract of M. oleifera has determined that it is very non-toxic. Such studies are performed to decide the adverse effects after a single dose and to find the median lethal dose (LD_{50}). The leaves were orally administered to rats at up to 2000 mg/kg and resulted in no mortality as part of the experimental investigations carried out in accordance with the Organization for Economic Co-operation and Development (OECD) Guideline 423. It was estimated that the LD_{50} is > 5000 mg/kg bw, so the plant could be considered as practically non-toxic. Observation was carried out for up to fourteen days and the animals exhibited normal feeding behavior, locomotor activity and grooming behavior and normal respiratory pattern.[12] There was no salivation, diarrhea, tremors, convulsions, lethargy or neurological abnormalities seen. Moreover, no significant difference was observed in the gross pathological examination of liver, kidney, heart, lung, spleen and gastrointestinal tract. All these findings point to a large window of opportunity for therapeutic use.Subacute toxicity studies can be useful to provide data on repeated administration for twenty eight days and are especially useful when assessing target organ toxicity.[12,13] Both aqueous and hydroalcoholic extract of leaves were found to be excellent tolerable even after repeated oral dose at the therapeutic dose as per OECD Guideline 407. The bodyweight gain, intake of feed and intake of water of the experimental animals were normal throughout the experimental period. Hematological values such as Hemoglobin, RBC, WBC, PLT, Differential Leucocyte Count were found to be in normal physiological range.[14] Liver enzymes (ALT, AST, AlP and bilirubin) were normal on biochemical tests. Similarly, at the same time, there were no significant differences regarding the renal function parameters such as serum creatinine, blood urea nitrogen and uric acid. No necrosis, inflammation or fibrosis was detected in the major organs through histopathological examination and there was no cellular degeneration.[15]Here, the results are solid when it comes to any and all doubts over the repeated therapeutic administration safety.The chronic toxicity studies are significant in assessing chronic

exposures. Additionally, moringa leaf preparations are found to have a favourable safety profile as confirmed by repeated dose 90-day studies according to OECD guideline 408. In the experimental treatment the animals that were fed with the extract (500mg/kg/day) had normal physiological growth and no deaths were recorded.[16] The weights of the organs were comparable with the untreated control and no pathological changes were found in the liver, kidneys, pancreas, spleen, lungs or heart.[15,16] All biochemical parameters of blood were found within normal limits for glucose metabolism, lipid and serum protein concentrations. However, some studies reported a decrease in the levels of markers of oxidative stress, thus suggesting an additional antioxidant effect of the long-term use. Based on results of these observations, it is believed that the leaf extract could be used for therapeutic purposes for extended periods of time without posing too much threat.[17]Of particular concern are reproductive and developmental toxicity, as some plant parts have bioactive compounds that may affect reproductive physiology. The leaves extracts of the therapeutic doses have resulted no negative effects on fertility, implantation, fetal growth and embryonic development from the available evidence.[18]Experimental studies conducted on pregnant Wistar rats fed with the leaf extracts throughout pregnancy demonstrated there was no congenital abnormality, maternal toxicity and the body weights of fetuses, skeleton and fertility indices were normal. Root and bark extracts, however, contain alkaloidal constituents that have uterotonic effect – stimulating uterine contractions. Such effects can lead to miscarriage or premature labor.[19] Therefore, preparations containing roots or bark should not be used in pregnant women, and the use of preparations containing roots or bark in women of reproductive age should not be used in therapy until adequate clinical evidence is available.Genotoxicity tests are carried out to see if a substance can damage DNA or abnormal changes in chromosomes occur. In several studies the mutagenic activity of leaf extracts of M. oleifera was tested with standardized assays. No Ames test was carried out that resulted in any Salmonella typhimurium strains being found to be mutagenic.[20] Similarly, micronucleus assays were carried out in mice and no micronucleus formation and chromosomal aberration was found after administering the leaf extracts. No detectable genetic changes were found in the bone marrow and hardly any DNA fragmentation. All the above results are evidence of non-genotoxicity of the leaf extracts of M. oleifera at therapeutic doses.[21]Interestingly, cytotoxicity studies have revealed selective anticancer activity against malignant cells and sparing normal tissues. The leaves extract in methanol was inhibitory towards breast cancer cell lines, colon cancer cell lines and liver cancer cell lines. Selective action is thought to be via induction of apoptosis, inhibition of cell proliferation and inhibition of oxidative stress pathways.[22] Importantly, normal fibroblast cells are not very sensitive, meaning that it is a therapeutic selectivity that could be beneficial when designing future drugs.However, M. oleifera has a number of anti-nutritional compounds which could lead to impaired nutrient uptake if consumed in high enough quantities. Phytates are one of the major antinutritional substances, which are known to chelate essential minerals like calcium, iron,

zinc and magnesium, thereby decreasing its bioavailability.[23]Oxalates may also help to create kidney stones in predispositions. The presence of a high level of saponins may interfere with uptake of nutrients from the intestinal tract and tannins are known to affect digestibility of proteins, which induces insoluble protein complexes to be formed.[24] In addition, glucosinolates break down into isothiocyanate which has both beneficial and potentially harmful effects at different doses. The traditional processing technique (boiling, blanching and fermentation and drying) has a positive effect towards reduction of anti-nutritional factors and improvement of bioavailability of nutrients.With the increasing popularity of moringa as a dietary supplement it has become increasingly important to consider herb–drug interactions. Several phytochemicals have been found in the plant that can interact with the metabolism of drugs, by regulating the metabolism of cytochrome P450 enzymes.[25]These interactions may cause other drugs that are used simultaneously to affect the body in a different way. Besides, Moringa possesses inherent, hypoglycemic and anti-hypertensive properties that might synergise the treatment effect of anti-diabetic and anti-hypertensive pharmaceuticals.[26]Simultaneous administration therefore may lead to excessive decreases of blood glucose or blood pressure. While it has not been definitely proven that there are any clinically important interactions, care should be taken, especially in patients on narrow therapeutic index drugs.[27]

Finally, it is worth noting that currently available toxicological data provide strong evidence for safe use of Moringa oleifera leaf preparations, under the recommended limit. Acute, subacute and chronic toxicity studies indicate a good safety profile and genotoxicity studies indicate little risk of DNA damage.[28]However, its reproductive toxicity has been a worry when preparations of the root and bark are taken. To ensure the safe implementation of moringa in modern healthcare systems, appropriate processing techniques, dosage recommendations based on scientific evidence, and comprehensive clinical studies are still crucial.[29]

4. Factors of Moringa oleifera safety

The therapeutic efficacy and safety of Moringa oleifera depends on a number of interdependent factors which affect the quality, biological activity and uniformity of the end product. Although a lot of research has confirmed the safety of moringa leaves, the variations in growing, processing, dose, and so forth can significantly contribute to the differences in phytochemical composition and consequently, pharmacological activity of moringa leaves.[30] These therefore need to be taken into account in the design of evidence based guidelines for safe and effective operation of these.All variables are not equal with dosage and time of exposure being the most important.[31] Several scientific studies have shown that moringa leaf preparations are safe if used within therapeutic dosages. However, excessive use of large quantities over a period of time may be associated with biochemical changes which are undesirable. Excessive intake of these supplements over the long-term may cause physiological stress as there have been some reports of slightly increased liver and kidney biomarkers.[32] Hence, it is imperative to set clear

dosage recommendations that have been supported by scientific findings, to reduce side effects and ensure maximum therapeutic benefits. Additional clinical studies are required to find optimum therapeutic windows for different populations of the population, including elderly, children, and pregnant women.Safety-effects strongly depend on plant part used as well.[33] The toxicological profile of moringa leaves and immature pods are the most favourable as the leaves are rich in nutrients and the toxic constituents are present in relatively small amounts. Roots and bark on the other hand, contain alkaloids and other secondary metabolites which may act on reproduction and neuro-toxicity. The root extracts have been shown to have uterotonic activity in experimental studies, and could lead to miscarriage in case of pregnancy.[34] Hence, when making commercial products, it is important to know the plant part used in their preparation to prevent accidental contact with possibly harmful constituents.Product quality and safety are also impacted by extraction and processing techniques.[35] The concentration of bioactive constituents can change depending on the extraction solvent, extraction temperature and time and post harvest handling. Indeed, hydroalcoholic extracts may have higher levels of flavonoids and phenolic compounds as compared to aqueous extracts and in turn led to improved biological activities. However, inadequate processing techniques can result in a more rapid degradation of phytochemicals and contamination with microorganisms.[36] Drying methods are of special importance as high temperatures can lead to loss of thermolabile components and low temperatures can encourage fungal growth. Hence, a standardized procedure in extraction of the seeds was important so as to ensure reproducible therapeutic results.The geographical and environmental conditions also affect the phytochemical variability.[37] The levels of nutrients and secondary metabolites are very dependent on soil composition, altitude, rainfall, seasonal changes and agriculture practices. Variations in antioxidant contents of Moringa plants grown in different areas have been shown. This variation may result in differences in how effective the treatment is or in side effects.[38]Thus, it is important to incorporate the geographical traceability and phytochemical profiling in the quality assurance.It is also highly essential to develop and maintain the product integrity by appropriate storage. Some bioactive compounds, which are not stable, are susceptible to oxidative degradation due to moisture, oxygen, heat and exposure to light.[39] What is worse, poor storage conditions could lead to microbiological contamination and the presence of fungi that can contain herbs with toxic elements, mycotoxins. There may also be pesticide, heavy metals and environmental pollutants during the growing, picking, transportation and packaging process. Therefore it is important to adhere to the Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) in the manufacture of these products to guarantee safety of consumer.[40]

5. Standardization of *Moringa oleifera*

Standardization is a scientific process which is being done systematically to find out the identity, purity, potencification, quality and consistency of herbal products. Unlike synthetic

drugs, medicinal plants are a highly variable, natural product and the content of phytochemicals are highly dependent upon environment and processing.[41] Therefore, it is essential to standardize all QC procedures with an aim to reach the same therapeutic results and regulatory approval.The outstanding nutritional and pharmacological properties of Moringa oleifera have led to its international recognition.[42]The different parts of the plant possess antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, cardioprotective, anticancer and immunomodulatory effects. However, if the products are to have a consistent phytochemical profile, this therapeutic potential can only be optimally tapped.[43] Thus, it is necessary to have extensive standardization protocol to make moringa a strong medicinal agent from its traditional herbal use.The initial process in the standardization is termed as Pharmacognostic evaluation. Macroscopic examination of the leaves reveals a dark green colour with a slight bitter smell and odour. Leaflets oval or ovate, with a smooth edge and pointed tip. Greyish-white, rough bark and triangular seed with 3 papery wings.[44] These morphological features give a preliminary authentication and prevent a substitute with another species.More diagnostic features are obtained from a microscopic examination. The leaves are arranged in a uniseriate epidermis and the leaves are covered with thick cuticle. The mesophyll is differentiated into two tissues such as palisade and spongy parenchyma. The lower epidermis is with many paracytic stomata.[45]Characteristic features that are useful for identification are spiral vessels, reticulate vessels, fibers and calcium oxalate crystals.The physicochemical analysis is another important aspect of quality control. The quantitative information on the product quality provided by moisture content, ash values, extractive values, pH, swelling index and foaming index.[46] To prevent microbial growth and maintain stability, the moisture content should be maintained at less than 10%. Total ash values can be used as an indication of inorganic matter and acid-insoluble ash as an indication of contamination with siliceous material. The extractive values with water and alcohol are an indication of the amount of soluble bioactive compounds. The above parameters are all quality assurance reference parameters.The Marker based standardization is increasingly applied in order to help achieving batch to batch consistency. The chemical markers identified are several bioactive compounds, such as quercetin, kaempferol, chlorogenic acid, rutin, niazimicin and isothiocyanate.[47] These compounds are directly related with plant's pharmacological activity and can be quantified with the aid of the newer analytical techniques. Other quality parameters used are the total phenolic and flavonoids contents which are also highly correlated with the antioxidant potential.The quality control of herbs has undergone a revolution with the use of modern analytical techniques. HPLC is one of the most accurate method for identification and quantification of phytochemicals.[48] Reverse-phase HPLC is appropriate for separation of flavonoids and phenolic acids for an accurate determination of marker compounds. HP-TLC is an efficient fingerprinting technique, where multiple samples can be analyzed at once. Characteristic chromatographic patterns, that give chemical signatures, and help to identify adulteration.[49]For

the identification of volatile compounds, fatty acids and terpenoids, gas chromatography-mass spectrometry is a valuable tool. It is a technique which has been successfully used to characterize important compounds such as phytol, oleic acid, linoleic acid and hexadecanoic acid. These constituents are known to be antioxidant, anti-inflammatory and cardioprotective.Second, important application of spectroscopy techniques is for standardisation. The total phenolics and flavonoids are quantified by UV-Vis spectroscopy in a short time. The identification of characteristic functional groups present in phytochemicals is done by Fourier Transform Infrared Spectroscopy and the detailed structural information of the major bioactive constituents of phytochemicals is done by Nuclear Magnetic Resonance Spectroscopy.[50] All the above techniques are used together to provide a complete chemical characterisation.But with the advent of DNA based authentication it has now come to be a formidable molecular tool in the field of botanical authentication.[51] DNA analysis is not influenced by environmental factors as is phytochemical analysis. Common genetic markers used for identification of the species are those which are universally distributed like rbcL, matK, internal transcribed spacer (ITS), trnH-psbA. Nowadays DNA barcoding is a valuable tool for the quality control in the herbal industry, and has contributed to discriminate among closely related species as well as to detect adulteration of powders with other products.[52] Other important tests for safety include microbiological and heavy metal testing. Microbial limits are acceptable with no pathogenic microorganisms such as: Escherichia coli, Salmonella spp, Staphylococcus aureus or Pseudomonas aeruginosa. To prevent chronic toxicity, heavy metals (lead, cadmium, arsenic and mercury) must not exceed World Health Organization guidelines.[53]Shelf life of products can be determined by stability studies. When stored under recommended storage conditions, the shelf life of Moringa oleifera leaf powder is 18-24 months.[54]Capsules containing antioxidant activity decline more or less slowly during storage, but if stored in darkness and under low temperatures (less than 25°C) in sealed containers, the antioxidant activity is fairly maintained and the content of phenolics and flavonoids decreases slowly.Collectively, these measures provide a scientific framework to ensure moringa-based products are of high quality and safe for use, and can be applied in a consistent way within the healthcare system.[55]

6. Future directions

Moringa oleifera is a promising plant for therapeutic and commercial applications; however, there are several scientific, technological and regulatory challenges for the complete integration of it into the evidence-based healthcare systems. Overcoming these difficulties is crucial in order to make this traditional medicinal plant a worldwide accepted pharmaceutical and nutraceutical resource.[56]One of the major concerns is the toxicity and/or safety of the different portions of the plant. While moringa leaves have shown excellent safety profile, the roots, bark

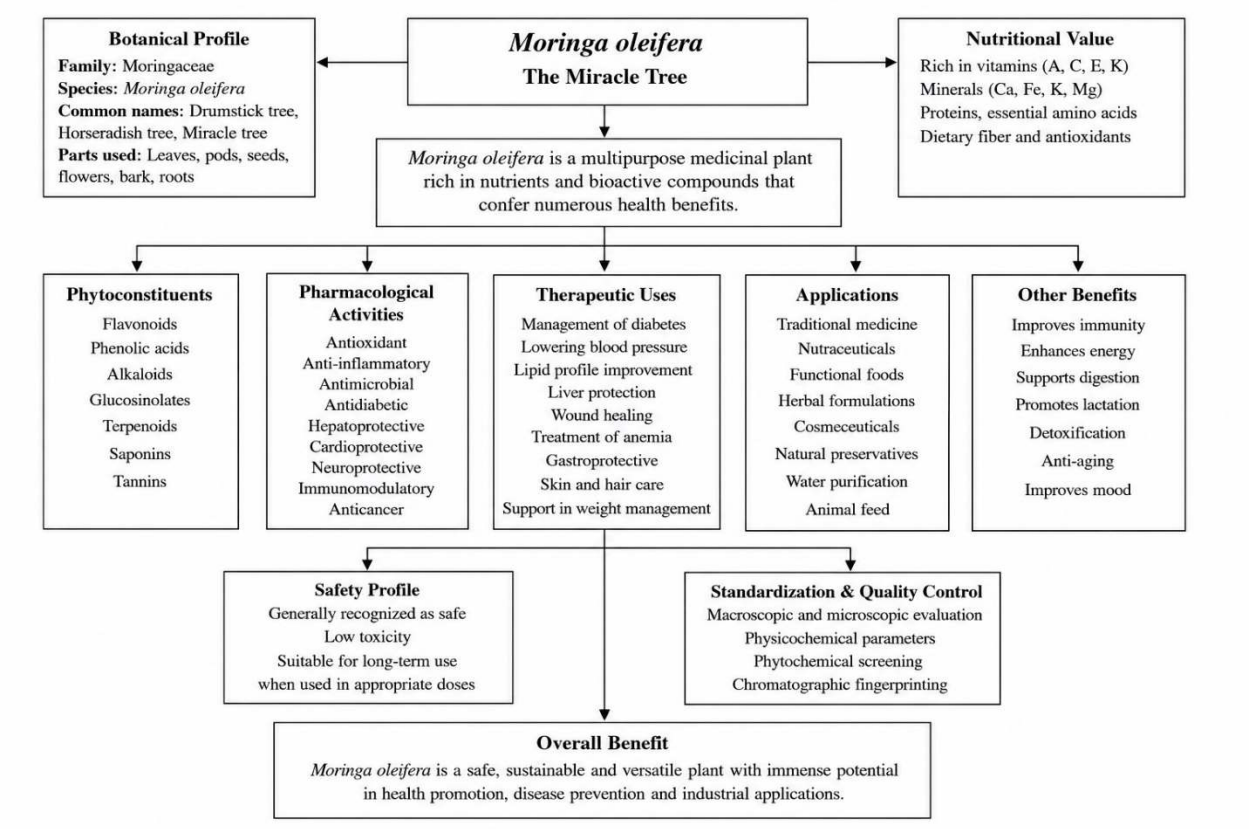
and some preparations of the seeds contain alkaloids and secondary metabolites which could bring about adverse physiological reactions.[57]An important issue of concern is reproductive toxicity as extracts of the root and bark are uterotonic and are able to induce uterine contractions which could lead to abortion.[58]Further, products that are concentrated powders or extracts can be easily over-dosed, particularly by individuals who think that herbal products are harmless. Hence, it is important to make evidence-based dosage recommendations and communicate to consumers about safe consumption practices.[59]Another significant barrier is the lack of good quality clinical evidence. Most of the pharmacology properties of Moringa oleifera (mostly anti-diabetic, anti-inflammatory, anti-oxidant, cardio protective and anti-cancer) are in vitro and animal based. The results are encouraging but will need to be replicated in humans to determine if they can be applied to people. There are many clinical studies, but they are short term, not well standardized with regards to plant materials and involve few patients.[60] Therefore, a lack of quality human evidence is a problem for health care providers and regulators, particularly when it comes to moringa based therapies.A second issue is the absence of harmonization of regulations that is a large challenge to commercialization.[61] Different countries have different regulations on herbal products. In some areas, moringa products are considered as "Dietary supplements" and in others as "Functional food products", "Traditional medicines" or "Novel food products". All these regulatory variation make trading internationally difficult, increase manufacturing costs and slow down product approval. A harmonized guideline internationally would be very helpful in order to enhance the global market and also to boost the consumers' confidence.[62]The product variability is also due to environmental and agricultural related factors. Phytochemical composition is greatly affected by climate change, soil degradation, pest infestation and rainfall changes. The amount of phytochemicals contained directly correlates to therapeutic effectiveness and environmental stress can cause great variability in product quality. [63]A large scale cultivation can also make the crops vulnerable to diseases and pest infestation threatening sustainable production on a large scale in the agriculture sector.The other big limitation is that there are no standard protocols. Geographical origin, harvest season and extraction and storage can cause significant differences in phytochemical profiles. Therefore, commercial products may have different results in terms of therapy.[64]Appropriate post harvest handling can also accelerate the loss of antioxidants, vitamins and proteins. Therefore, an integrated standardization program is necessary, comprising analytical fingerprinting, molecular authentication systems and quality assurance systems.Another factor that is of concern is the anti-nutritional factors.[65]These phytates, oxalates, tannins and saponins in the gastrointestinal tract can be responsible for lowering the bioavailability of essential nutrients. These compounds can be significantly reduced by processing techniques, but still need to be optimized to get the greatest nutritional benefits and least negative impacts.[67]The potential for Moringa oleifera is however still relatively good. One of the most promising ones is the use of it in pharmaceutical drug

discovery. A large number of bioactive compounds have been shown to have multitargeted therapeutic effects on chronic non-communicable diseases. The isothiocyanate, flavonoids and polyphenols are under study as the primary molecules for designing new therapeutic agents to treat metabolic disorders, liver diseases, inflammatory diseases and various cancers.[68]The other important area of research has emerged is drug delivery system with nanotechnology. Most of the phytochemicals present in Moringa are poorly soluble in water, are poorly bioavailable and are metabolized very rapidly. To enhance their stability, absorption and therapeutic effect, they can be formulated in a nanocarrier, for instance, liposomes, nanoemulsions, polymeric nanoparticles or solid lipid nanoparticles. These advanced drug delivery systems can improve delivery to target tissues, decrease the dosage and minimize side effects.[69]Standardisation will also play an important role in the future in commercialisation of herbal medicines. HPLC, HPTLC, GC-MS, FTIR, NMR and DNA Barcoding can be incorporated in the quality control lab practice to ensure batch to batch uniformity and authenticity of the product. All these analytical platforms can provide reproducible and reliable phytochemical fingerprinting which will ensure therapeutic reproducibility and preclude adulteration.Another burgeoning market in which moringa is used is cosmetics and personal care.[70]Moringa seed oil is very stable to oxidation and has moisturizing properties, which makes it a good ingredient for anti-aging creams, serums and sunscreens, as well as hair care products. Moreover, it also has antioxidant and antimicrobial properties, which further boost its dermatological use.[71]Future studies should also be emphasized and they must be large scale, multicenter, randomized clinical trials. These studies are required to determine accurate dosage recommendations, determine long-term safety and to see if there is any herb-drug interaction. Finally, support should be provided to integrate moringa into traditional medicine with clinical evidence to determine the potential integration of moringa into mainstream medicine.[72]Moreover, Moringa oleifera has a huge potential to be used as functional food and for public health nutrition programmes.[73] The fortification with Moringa leaf powder can be a cost-effective method to fight against PEM, IDA and micronutrient deficiencies especially in the developing world. In addition, it has other multifaceted applications such as sustainable agriculture, production of organic fertilizers, animal feed and production of biofuels and water purification technologies, all aspects that make it relevant to society.[74]

7. Conclusion

Moringa oleifera can be one of the most promising medicinal plants of the 21st century due to its nutritional value and pharmacological activities. It is highly rich in bioactive compounds including vitamins, minerals, essential amino acid as well as flavonoids and phenolic acids and has a broad spectrum of therapeutic applications in the treatment of various chronic diseases

such as diabetes mellitus, cardiovascular diseases, inflammatory diseases, oxidative stress-induced diseases and liver dysfunction.



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