Therapeutic and Nutraceutical Horizons of Moringa oleifera Lam.: A Comprehensive Review of Bioactive Mechanisms in Chronic Disease Modulation

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Abstract- ***Moringa oleifera Lam., an indegeneous fast growing deciduous tree of the Himalayan foothills in northern India, has received increasing attention for its excellent nutritional and medicinal characteristics. This tropical species belongs to the Moringaceae family and is full of health-promoting nutrients, protein, vitamin A, important minerals, amino acids and various phenolics including powerful antioxidants, flavonoids and isothiocyanates. In recent years, its anti-inflammatory, antioxidant, anticarcinogen, hepatoprotectant, neuroprotective, hypoglycemic and hypolipidemic activities have also been established by scientific studies. These therapeutic effects are mainly attributed to its wide range of phytochemical contents, particularly flavonoids and isothiocyanates. In this integrative review, we present current scientific reports on the pharmacological effects and their mechanisms of M. oleifera, with special attention to chronic diseases including inflammation-related conditions, diabetes, neuro degenerative disorders, and cancer. These findings highlight its perspective as a natural remedies long-term care and treatment of some chronic human diseases.***

Indexed Terms- ***Moringa oleifera, Bioactive phytochemicals, Chronic disease prevention, Anti-inflammatory mechanisms, Antioxidant defense, Nutraceutical therapeutics***

I. INTRODUCTION

Moringa oleifera Lam., also known as the drumstick tree or horseradish tree, belongs to the Moringaceae family and is widely used around the world as both food and medicinal plant. [1]. Its leaves are an excellent source of essential micronutrients such as beta-carotene (a provitamin A), vitamin C, vitamin E, and polyphenolic compounds, and thus it is very good natural source of antioxidants [2]. Emerging evidence indicates that M. oleifera provides a wide spectrum of health benefits including for instance anti-inflammatory and anticancer effects, liver and brain health protection 1[4]. Scientific evidence also supports its use for diabetes, arthritis, cardiovascular disease, infertility, pain, depression and thyroid conditions 5.

In response to growing evidence supporting these effects, there is an increased scientific interest in further studying the pharmacological effects of grape powder and its underlying biological action. In this paper, we review recent advances in the literature on M. oleifera, with emphasis on the nutritional and medical potential, mechanisms of molecular interactions, and prospective applications to treat and/or to preclude different diseases that are related with chronic inflammation.

II. ANTIMICROBIAL PROPERTIES

Studies in the literature have consistently reported that various parts of Moringa oleifera, such as leaves, roots, bark, and seeds, have shown strong antimicrobial activity against a broad range of pathogens [7–12]. For instance, a water-soluble lectin from the seeds of M. oleifera has been demonstrated to inhibit growth as well as integrity of a variety of pathogenic bacteria through breakdown of their cell membrane [9]. In addition, the roots contain a bioactive compound pterygospermin and the latter can serve as an antibacterial and an antifungal agent [12].

Another compound, deoxy-niazimicine aglycone extracted with chloroform from ethanol extracted root bark exhibited significant antimicrobial activity [10]. Even more interesting, the juice of the stem bark also exhibited effectiveness against Staphylococcus aureus, a common known Gram-positive bacteria [8]. As for leaf extracts, inhibitory effects towards Gram-positive bacteria (S. aureus and Enterococcus faecalis) are stronger against a variety of Gram-negative bacteria such as Escherichia coli, Salmonella, Pseudomonas aeruginosa, Vibrio parahaemolyticus, and Aeromonas caviae [11].

Further, the toothpaste formulated with leaf extract showed better inhibitory activities against S. aureus and S. mutans compared to some commercialized mouthwashes proving that the antimicrobial potential of M. oleifera remains in personal care industry (Marbaniang et al. [10]).

III. ANTI-INFLAMMATORY EFFECTS

The body response to infection or injury by means of the immune system is inflammation. Nevertheless, when inflammation is long-term, it may be associated with human diseases including diabetes type 1 or 2, cancer, autoimmune responses, and cardiovascular diseases [13–15]. Proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β) can induce the production of cytotoxic mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2), through the action of enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), respectively [16].

Previous studies have reported that M. oleifera extracts exhibit remarkable anti-inflammatory activity. They attenuate the expression of TNF-α, IL-6, and IL-8 in human monocyte-derived macrophages after exposure to inflammatory stimuli, including lipopolysaccharide (LPS) and cigarette smoke extract [17]. They also inhibit NF-κB, a master regulator of inflammation.

In animal models, oral administration of hydro-alcoholic extracts of M. oleifera seeds considerably decreased colon inflammation, crypt damage and the activity of enzymes related to tissue damage in chemically induced colitis in rats [18]. This may point to the possibility of M. oleifera activity in treatment of pathologies such as inflammatory bowel disease.

In addition, through cell culture, the present extracts of M. oleifera reduce iNOS and COX-2 expression, and improve anti-inflammatory cytokines such as IL-10 in a dose-responsive fashion. This two-way balance helps to mitigate inflammation whilst supporting the healing process 19.

One of the active anti-inflammatory molecules, 4-[(2-O-acetyl-α-L-rhamnosyloxy)benzyl] isothiocyanate (RBITC), was isolated and characterized in the study. It functions by suppressing upstream signaling cascades such as mitogen-activated protein kinases (MAPKs) and NF-κB [21]. Swelling as that due to aspirin could be observed with isothiocyanate rich seed extract (MSE) in rat model. MIC-1 (moringa isothiocyanate-1) alone at 10 μM significantly was more promising than curcumin in the induction of antioxidant genes such as NQO1, GSTP1, and HO-1 [22].

Clinical observations additionally support these results. In one small human trial, 66.67% of urinary tract infection patients who were treated with M. oleifera root bark extract were fully cured in three weeks, surpassing the results of the control group [23]. These findings support the use of M. oleifera in traditional management of inflammation.

The underlying biological mechanisms are summarized in the schematic representation (Figure 1) of the original article that depicts how M. oleifera modulates the inflammatory effectors and signaling molecules including TLR4, NADPH, IκB, KEAP1, NF-κB, COX-2, iNOS, and cytokines TNF-α IL-6 and IL-1β.

IV. ANTIOXIDANT AND HEPATOPROTECTIVE ACTIVITIES

Polyphenol-rich natural compounds are a known group of compounds to counteract oxidative stress through scavenging of free radicals [24–26]. Moringa oleifera is a unique botanicals for its high antioxidant content. A high level of antioxidant activity in the

leaves was found in term of the methanol extract and for its antioxidant constituents chlorogenic acid, rutin, quercetin glycoside and kaempferol rhamnoglucoside. In the same vein, its roots and stem bark were reported to be rich in procyanidins, a class of antioxidants [27].

Due to its polyphenols-rich nature, M. oleifera exhibits substantial antioxidant activity of free radical scavenging properties in both older and young leaves 28. This antioxidant potential has been demonstrated in various in vivo research. For example, the administration of M. oleifera leaf extract on a daily basis for 15 days to a Swiss albino mouse model of radiation-induced oxidative stress led to the recovery of reduced glutathione (GSH) levels and inhibition of lipid peroxidation in the liver thereby preventing oxidative stress 30.

The protective effects are also effective on the chemical induced liver toxicity. In rats administered with paracetamol (PCM) toxic dose, pre-treatment with M. oleifera extract ameliorated the oxidative damage, restored the enzyme levels, including GST, GPx, and GR, and results were similar to the standard liver protective drug silymarin [32–34].

Pretreatment of rats with M. oleifera leaves also protected against liver damage induced by CCl_4, and this could be attributed to the phyto-concentration of phenolic compounds (quercetin, beta-sitosterol, and kaempferol) [35]. Also, it afforded antioxidant against hepatic toxicity of cadmium and drug-induced hepatotoxicity triggered by antituberculosis treatment including isoniazid, rifampicin and pyrazinamide by normalizing liver enzymes (AST, ALT, ALP) and reducing lipid peroxidation [36].

M. oleifera leaves exerted a hepato-protective effect, as it prevented histopathological perturbations and restored endogenous antioxidant enzymes in a mouse model of high-fat diet [37]. Taken together, these data confirm that the plant not only prevents, but repairs liver oxidative injury.

V. NEUROPROTECTIVE POTENTIAL

With an aging population, the prevalence of neurodegenerative diseases, including Alzheimer's (AD), Parkinson's (PD) and Huntington's Disease (HD) is increasing. These are frequently associated with oxidative stress, leading to mitochondrial dysfunction and injury to neurons by lipid, protein, and DNA oxidation [38–41]. As there are only limited pharmacological approaches to stop those conditions or to slow or reverse these conditions, researchers are beginning to rely on antioxidant plant-derived molecules [42].

Leaves of M. oleifera have potential to protect the brain. In a rat model that mimics Alzheimer's disease, the use of alcohol-based extract of leaves served against oxidative stress, and maintained the brain health of the rats [43]. In another report in the MPTP-induced Parkinsonism model in mice, seed derived ITCs not only reduced inflammation, but also protected neurons from oxidative and apoptotic damage suggesting their bi-functional protective effect [44].

Aside from the protection against disease, M. oleifera also leads to an amplification of nerve cell growth. In vitro, ethanolic leaf extracts enhanced neurite outgrowth, dendrite branching and synapse formation in developing neurons [45]. In animal studies, the extract promoted memory and prevented the loss of neurons in important areas of the brain such as the hippocampus – additionally, it reduced indicators of oxidative stress and inflammation [46].

In rats exposed to aluminum chloride (producing brain damage similar to dementia), M. oleifera (300 mg/kg) treatment induced a preservation of the temporal cortex of brain, after daily administration for 4 weeks. It down-regulated the expression of neuron-specific enolase (NSE) and glial fibrillary acidic protein (GFAP) that are the marker of neural injury [47].

M. oleifera could have the potential to reduce depression as well as its cognitiv eimproving effect. It also showed enhanced mood behavioral reversal in combination with fluoxetine, a common antidepressant, in animal models. This may be related to its action on the noradrenergic and serotonergic neurotransmission at a central level [48]. These encouraging results indicate the potential of M.

oleifera as a natural substitute or cocure for the treatment of neurodegenerative and mood disorders.

VI. ANTICANCER EFFECTS

Cancer is still one of the major causes of death worldwide and resistance to the existing treatments and toxic effects of the drug are major problems for the treatment [49]. Curiously enough routine intake of cruciferous have been associated with decreased risks of cancer such as breast, lung and colon cancer 50. Among these plants, Moringa oleifera has been reported to exhibit anticancer potential. Leaves and bark extracts have been reported to suppress the growth of various cancer cell lines such as human breast, pancreatic and colorectal cancer [52]. A GC-MS chemical analysis of Moringa extracts found that twelve bioactive compounds have been determined, three of which potentially have direct anticancer effects [52]. It is likely due to its multi-pronged strategy hindering cell division, inducing cancer cell death, inhibiting pathways that allow tumors to push forward, increasing the body's ability to detox, and synergistically enhancing existing chemotherapy drugs [53]. Importantly, isothiocyanates are well known to possess anticancer activities which are hydrolyzed products of glucosinolates by the enzyme myrosinase [54].

Anti-cancer activities of various isothiocyanates have been reported. For example, allyl isothiocyanate (AITC) inhibited growth in hormone-sensitive and hormone-insensitive PCa cells, by blocking the cell cycle progression and inducing apoptosis [55]. In a mice model, benzyl isothiocyanate (BITC) decreased the size of pancreatic tumors and downregulated the expression of cancer key proteins such as AKT, PI3K, and mTOR [56]. Even though the research on moringa-unique isothiocyanates is fairly new, as of now, there is chances of their potential anticancer effects are feasible.

6.1. Inhibiting Cancer Cell Growth

It has been reported that M.oleifera preferentially suppress the growth of multiple human cancer cell lines, including A549 (lung cancer), HepG2 (liver cancer), MDA-MB-231 (breast cancer), and HCT-8 (colon cancer) [52, 57]. Notably, it could induce up to 95% inhibitory effect on the proliferation of SH-SY5Y neuroblastoma cells. The extract also caused definite morphological and DNA fragmentation(KB cell: oral cancer cell) which indicate that the product had strong anti-proliferative effects[58].

6.2. Apoptosis Induction and Cell Cycle Arrest

Apoptosis (programmed cell death) is an essential mechanism for clearing damaged or neoplastic cells. M. oleifera has been shown to induce apoptosis by up-regulating caspase signaling pathways and blocking cell cycle progression 58.

In M. oleifera–treated lung cancer (A549) cells, the proportion of sub-G1-cell population, which indicates the occurrence of apoptosis, and the expression of cleaved caspase-3 in a dose-dependent manner was elevated [60]. Equivalent apoptotic impacts were observed in A2058 (melanoma) cells, in which stress-responsive kinases (p-JNK and p-ERK) were also activated by the compound without altering their protein expression (total) [61].

In cholangiocarcinoma (bile duct cancer) cells, the seed extract also elevated phosphorylation of ERK1/2 and p38 MAPK, suggesting preferential engagement of pro-apoptotic cascades [62]. These effects are likely due to the action of active ingredients such as eugenol, D-allose, isopropyl isothiocyanate, and fatty acid esters [52].

In addition, M. oleifera can arrest the cell cycle at G2/M phase to prevent damaged cells from continuing to divide. It was demonstrated by cyclin D1 downregulation in pancreatic cancer cells (PANC-1) and a higher sub-G1 cell fraction and decreased expression of NF-κB-related proteins (p65, p-IκBα, IκBα) [53].

6.3. Enhancing Chemotherapy

Drug resistance (DR) is one of most important obstalces in cancer treatment. Natural therapeutic agents such as M. oleifera could serve as a safer alternative for overcoming MDR owing to its low tox-

icity, multiple cellular targets and few side effects [65].

Surprisingly, the M. oleifera leaves/callus extracts plus doxorubicin significantly increased cell death of cancer cells (HeLa) compared to either doxorubicin treatment alone. This combinatory effect indicates the potential benefit of combining M. oleifera with conventional chemotherapy to enhance the therapeutic response [66].

6.4. Regulation of Detoxification Enzymes

The enzymes of detoxification (eg, cytochrome P450 and glutathione-S-transferase [GST]) are the important chemical defense against carcinogens. Several studies revealed that both M. oleifera extracts restore or increase these enzymes activity, providing an increase in the ability to remove harmful compounds from the body 67.

For instance, pod extracts and isolated saponins from M. oleifera have been shown to serve as potent chemoprotective agents against DMBA-induction of renal tumorigenesis in mice perhaps by scavenging ROS and protecting detox pathways [70]. Hydro-alcoholic extracts also potentiated I and II phase detoxifying enzymes thus representing M. oleifera as a powerful modulator of xenobiotics metabolism [69].

VII. REGULATING BLOOD SUGAR LEVELS

Diabetes mellitus (DM) is a metabolic disorder that is becoming an increasingly significant health issue worldwide, characterized by high blood glucose (hyperglycemia). The leaves of Moringa oleifera have traditionally been used in diabetes treatment, and modern day studies are rapidly coming to a conclusion with increasing scientific information [71].

In diabetic rats (Goto-Kakizaki; GK rats type 2 model diabetes), M. oleifera was discovered to improve glucose handling [72]. Fruit extracts (fruit n-butanol extract-Table 2) rich in bioactive compounds, such as N-benzyl thiocarbamates, carbamates, and benzyl nitriles, could increase the insulin secretion from pancreatic beta cells[73], inhibit the activity of inflammatory enzymes (cyclooxygenases), and reduce the oxidative damage.

It has been demonstrated in various animals that administration of M. oleifera extracts led to a decrease of the raised blood glucose level and was not associated with its apparent toxicity which indicated its safety and therapeutic potential [74]. In addition, the daily treatment with water extract of leaves at 100 mg/kg was found to potentiate insulin sensitivity and antioxidant defense in addition to favor immune reactivity and the control of blood glucose [75].

M. oleifera has been found to reduce glucose intolerance and to have a protective effect against diabetic complications in other studies as well. For instance, leaf extract administered as treatment for six weeks prevented diabetes-induced renal inflammation and structural damage in rats [77]. Moreover, seed powder treated diabetic nephropathy and reversed normal histological organization in kidney and pancreas tissues of the animals 78.

Overall, these results indicate that M. oleifera would have potential to contribute to the regulation of glycemia and the prevention or attenuation of chronic complications of diabetes.

VIII. FUTURE OPPORTUNITIES AND NEW DEVELOPMENTS

Color or b/w Western blots show that autophagy is an important endogenous process clearing damaged organelles and proteins. This self-cleaning mechanism can be activated by numerous stimuli, such as lack of nutrients, endoplasmic reticulum (ER) stress or exposure to certain drugs [79]. Autophagy impairments are implicated in many diseases, such as infection, inflammation, neurodegeneration, aging, and cancer [80–83].

Stimulation of autophagy may thus enable cells to better survive stress and decrease their susceptibility to death-inducing stress [84]. Recently, plant-derived compounds such as resveratrol, curcumin, and quercetin have gained increasing attention as autophagy inducers for health promotion and life extension.

In view of the abundant phytochemicals found in M. oleifera and its very high safety, the prospects of it triggering autophagy are beginning to be investigated. If confirmed, this might open as a possibility the use or M. oleifera as a not only a supplement or traditional remedy, but as a scientifically supported remedy to deal with a plethora of chronic diseases.

CONCLUSION

Moringa oleifera appears to be an extraordinary representative of botanical flora with an immense and versatile pharmacological potential. Bioactive compounds such as flavonoids and isothiocyanates provide numerous health benefits. As a strong anti-inflammatory effect, it involves regulating important pathways such as N F-κB and PI3K/Akt. Its antioxidant properties counteract oxidative stress and, as a neuroprotector, it offers the possibility of inhibiting the course of neurodegenerative diseases.

The plant also has potent anticancer effects controlling cell proliferation, apoptosis promotion, cell cycle arrest and potentiation of chemotherapeutic action. In addition, M. oleifera has a hepato-protective effect and is supportive of glycemic regulation, which potentially make it a natural agent in the treatment of metabolic diseases including diabetes.

Despite these encouraging discoveries, much remains unknown concerning the molecular mechanisms of M. oleifera. Further investigation, especially at clinical stages, is required to confirm these findings and able to take full advantage of its pharmacological properties. Given its numerous health benefits and virtually no side effects, M. oleifera is undoubtedly a nutraceutical and medicinal intervention for the prevention and/or treatment of many chronic diseases.

REFERENCES

[1] Anwar, F., Latif, S., Ashraf, M., & Gilani, A.H. (2007). *Moringa oleifera*: A food plant with multiple medicinal uses. *Phytotherapy Research*, 21(1), 17–25.

[2] Mahmood, K.T., Mugal, T., & Haq, I.U. (2010). *Moringa oleifera*: A natural gift—A review. *Journal of Pharmaceutical Sciences and Research*, 2(11), 775–781.

[3] Abdull, R.A., Ibrahim, M.D., & Kntayya, S.B. (2014). Health benefits of *Moringa oleifera*. *Asian Pacific Journal of Cancer Prevention*, 15(20), 8571–8576.

[4] Posmontier, B. (2011). The medicinal qualities of *Moringa oleifera*. *Holistic Nursing Practice*, 25(2), 80–87.

[5] Banji, O.J., Banji, D., & Kavitha, R. (2012). Immunomodulatory effects of alcoholic and hydroalcoholic extracts of *Moringa oleifera* Lam. leaves. *Indian Journal of Experimental Biology*, 50, 270–276.

[6] S. Mishra, S. Lakhawat, and H. Pandey, "Moringa oleifera: A Miracle Plant," *Popular Kheti*, vol. 8, no. 2, pp. 29–30, 2020.

[7] Ariel, A., & Serhan, C.N. (2007). Resolvins and protectins in the termination program of acute inflammation. *Trends in Immunology*, 28(4), 176–183.

[8] Bhatelia, K., Singh, K., & Singh, R. (2014). TLRs: Linking inflammation and breast cancer. *Cellular Signalling*, 26(11), 2350–2357.

[9] Aggarwal, B.B. (2004). Nuclear factor-kappaB: The enemy within. *Cancer Cell*, 6(3), 203–208.

[10] Kou, X., Qi, S., Dai, W., Luo, L., & Yin, Z. (2011). Arctigenin inhibits lipopolysaccharide-induced iNOS expression in RAW264.7 cells through suppressing JAK-STAT signaling. *International Immunopharmacology*, 11(8), 1095–1102.
17–23. Refer to original article for detailed inflammation-related studies.

[11] Niedzwiecki, A., et al. (2016). Anticancer efficacy of polyphenols and their combinations. *Nutrients*, 8(9), 552.

[12] Thapa, A., & Carroll, N.J. (2017). Dietary modulation of oxidative stress in Alzheimer's disease. *International Journal of Molecular Sciences*, 18(7), 1583.

[13] Zhang, S.F., et al. (2014). Autophagy-associated targeting pathways of natural products during cancer treatment. *Asian Pacific Journal of Cancer Prevention*, 15(24), 10557–10563.

[14] Atawodi, S.E., et al. (2010). Evaluation of polyphenol content and antioxidant properties of methanol extracts of *Moringa oleifera* leaves,

stem, and root barks. *Journal of Medicinal Food*, 13(3), 710–716.

[15] Verma, A.R., et al. (2009). In vitro and in vivo antioxidant properties of different fractions of *Moringa oleifera* leaves. *Food and Chemical Toxicology*, 47(9), 2196–2201.

[16] Sreelatha, S., & Padma, P.R. (2009). Antioxidant activity and total phenolic content of *Moringa oleifera* leaves in two stages of maturity. *Plant Foods for Human Nutrition*, 64(4), 303–311. 30–37. Refer to original article for detailed hepatoprotective studies.

[17] Prince, M., et al. (2013). The global prevalence of dementia: A systematic review and meta-analysis. *Alzheimer's & Dementia*, 9(1), 63–75. 39–42. See original article for oxidative stress and neurodegeneration studies.

[18] Ganguly, R., & Guha, D. (2008). Protection by *Moringa oleifera* in a rat model of Alzheimer's disease. *Indian Journal of Medical Research*, 128, 744–751.

[19] Giacoppo, S., et al. (2017). The isothiocyanate isolated from *Moringa oleifera* shows potent anti-inflammatory activity in subacute Parkinson's disease. *Rejuvenation Research*, 20(1), 50–63.

[20] Hannan, M.A., et al. (2014). *Moringa oleifera* with neuronal survival and neurite outgrowth promoting potential. *Journal of Ethnopharmacology*, 152(1), 142–150.

[21] Sutalangka, C., et al. (2013). *Moringa oleifera* mitigates memory impairment in dementia model. *Oxidative Medicine and Cellular Longevity*, 2013, 695936.

[22] Ekong, M.B., et al. (2017). Neuroprotective effect of *Moringa oleifera* against aluminum-induced cortical degeneration. *Metabolic Brain Disease*, 32(5), 1437–1447.

[23] Kaur, G., et al. (2015). Evaluation of antidepressant activity of *Moringa oleifera*. *Journal of Ayurveda and Integrative Medicine*, 6(4), 273–279.

[24] Siegel, R., et al. (2012). Cancer statistics for Hispanics/Latinos, 2012. *CA: A Cancer Journal for Clinicians*, 62(5), 283–298.

[25] Boggs, D.A., et al. (2010). Fruit and vegetable intake and breast cancer risk. *American Journal of Epidemiology*, 172(11), 1268–1279.

[26] Fowke, J.H., et al. (2003). Urinary isothiocyanate levels, brassica, and human breast cancer. *Cancer Research*, 63(14), 3980–3986. 52–53. See original article for anticancer studies involving *Moringa*.

[27] Fahey, J.W., et al. (2001). Diversity and distribution of glucosinolates and isothiocyanates. *Phytochemistry*, 56(1), 5–51.

[28] Xiao, D., et al. (2003). Allyl isothiocyanate inhibits prostate cancer cells. *Carcinogenesis*, 24(5), 891–897.

[29] Gao, N., et al. (2011). Phenethyl isothiocyanate exhibits antileukemic activity. *Cell Death & Disease*, 2(4), e140. 57–62. Refer to original article for detailed molecular anticancer mechanisms. 63–64. General sources on apoptosis and cell cycle arrest in cancer.

[30] Kou, X., et al. (2017). Molecular targets of ampelopsin in cancer prevention. *Anti-Cancer Agents in Medicinal Chemistry*, 17(12), 1610–1616.

[31] Jafarain, A., et al. (2014). Cytotoxicity of *Moringa oleifera* extracts on HeLa cells. *Advanced Biomedical Research*, 3, 194.

[32] Singh, R.P., et al. (2000). Effects of *Justicia adhatoda* on enzymes and lipid peroxidation. *Molecular and Cellular Biochemistry*, 213(1–2), 99–109.

[33] Sharma, V., et al. (2012). Chemopreventive efficacy of *Moringa* pods in carcinogenesis. *Asian Pacific Journal of Cancer Prevention*, 13(6), 2563–2569.

[34] Bharali, R., et al. (2003). Chemomodulatory effect of *Moringa oleifera*. *Asian Pacific Journal of Cancer Prevention*, 4(2), 131–139.

[35] Sharma, V., & Paliwal, R. (2014). Chemoprevention by *Moringa* saponin against renal cancer. *Indian Journal of Clinical Biochemistry*, 29(2), 202–209.

[36] Grover, J.K., et al. (2002). Indian medicinal plants with anti-diabetic potential. *Journal of Ethnopharmacology*, 81(1), 81–100.

[37] Kar, A., et al. (2003). Hypoglycaemic activity of Indian plants in diabetic rats. *Journal of Ethnopharmacology*, 84(1), 105–108.

[38] Mbikay, M. (2012). Therapeutic potential of *Moringa oleifera* in hyperglycemia and dyslipidemia. *Frontiers in Pharmacology*, 3, 24.

[39] Omabe, M., et al. (2014). Ethanolic extract of *Moringa* in diabetic rats. *Journal of Toxicology*, 2014, 406242.

[40] Tuorkey, M.J. (2016). Effects of *Moringa* aqueous extract in diabetic mice. *Interventional Medicine & Applied Science*, 8(3), 109–117. 76–78. See original article for studies on diabetic nephropathy.

[41] Finkel, T., & Holbrook, N.J. (2000). Oxidants, oxidative stress and the biology of aging. *Nature*, 408(6809), 239–247.

[42] Kou, X., & Chen, N. (2017). Resveratrol as a natural autophagy regulator for prevention and treatment of Alzheimer's disease. *Nutrients*, 9(9), 927.

[43] Ganguly, R., & Guha, D. (2008). Alteration of brain monoamines & EEG wave pattern in rat model of Alzheimer's disease & protection by *Moringa oleifera*. *Indian Journal of Medical Research*, 128(6), 744–751.

[44] Giacoppo, S., Rajan, T.S., De Nicola, G.R., Iori, R., Rollin, P., Bramanti, P., & Mazzon, E. (2017). The isothiocyanate isolated from *Moringa oleifera* shows potent anti-inflammatory activity in the treatment of murine subacute Parkinson's disease. *Rejuvenation Research*, 20(1), 50–63.

[45] Hannan, M.A., Kang, J.Y., Mohibbullah, M., Hong, Y.K., Lee, H., Choi, J.S., Choi, I.S., & Moon, I.S. (2014). *Moringa oleifera* with promising neuronal survival and neurite outgrowth promoting potentials. *Journal of Ethnopharmacology*, 152(1), 142–150.

[46] Sutalangka, C., Wattanathorn, J., Muchimapura, S., & Thukham-mee, W. (2013). *Moringa oleifera* mitigates memory impairment and neurodegeneration in an animal model of age-related dementia. *Oxidative Medicine and Cellular Longevity*, 2013, 695936.

[47] Ekong, M.B., Ekpo, M.M., Akpanyung, E.O., & Nwaokonko, D.U. (2017). Neuroprotective effect of *Moringa oleifera* leaf extract on aluminium-induced temporal cortical degeneration. *Metabolic Brain Disease*, 32(5), 1437–1447.

[48] Kaur, G., Invally, M., Sanzagiri, R., & Buttar, H.S. (2015). Evaluation of the antidepressant activity of *Moringa oleifera* alone and in combination with fluoxetine. *Journal of Ayurveda and Integrative Medicine*, 6(4), 273–279.

[49] Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics for Hispanics/Latinos, 2012. *CA: A Cancer Journal for Clinicians*, 62(5), 283–298.

[50] Boggs, D.A., Palmer, J.R., Wise, L.A., Spiegelman, D., Stampfer, M.J., Adams-Campbell, L.L., & Rosenberg, L. (2010). Fruit and vegetable intake in relation to risk of breast cancer in the Black Women's Health Study. *American Journal of Epidemiology*,

[51] Fowke, J.H., Chung, F.L., Jin, F., Qi, D., Cai, Q., Conaway, C., Cheng, J.R., Shu, X.O., Gao, Y.T., & Zheng, W. (2003). Urinary isothiocyanate levels, brassica, and human breast cancer. *Cancer Research*, 63(14), 3980–3986.

[52] Al-Asmari, A.K., Albalawi, S.M., Athar, M.T., Khan, A.Q., Al-Shahrani, H., & Islam, M. (2015). *Moringa oleifera* as an anti-cancer agent against breast and colorectal cancer cell lines. *PLoS ONE*, 10(8), e0135814.

[53] Berkovich, L., Earon, G., Ron, I., Rimmon, A., Vexler, A., & Lev-Ari, S. (2013). *Moringa oleifera* aqueous leaf extract down-regulates NF-κB and increases the cytotoxic effect of chemotherapy in pancreatic cancer cells. *BMC Complementary and Alternative Medicine*, 13, 212.

[54] Fahey, J.W., Zalcmann, A.T., & Talalay, P. (2001). The chemical diversity and distribution of glucosinolates and isothiocyanates among plants. *Phytochemistry*, 56(1),

[55] Xiao, D., Srivastava, S.K., Lew, K.L., Zeng, Y., Hershberger, P., Johnson, C.S., Trump, D.L., & Singh, S.V. (2003). Allyl isothiocyanate, a constituent of cruciferous vegetables, inhibits proliferation of human prostate cancer cells. *Carcinogenesis*, 24(5), 891–897.

[56] Gao, N., Budhraja, A., Cheng, S., Liu, E.H., Chen, J., Yang, Z., Chen, D., Zhang, Z., & Shi, X. (2011). Phenethyl isothiocyanate exhibits antileukemic activity by inactivation of Akt and activation of JNK pathways. *Cell Death & Disease*, 2(4), e140.

[57] Karim, N.A., Ibrahim, M.D., Kntayya, S.B., Rukayadi, Y., Hamid, H.A., & Razis, A.F. (2016). *Moringa oleifera* Lam: Targeting

chemoprevention. *Asian Pacific Journal of Cancer Prevention*, 17(8), 3675–3686.

[58] Sreelatha, S., Jeyachitra, A., & Padma, P.R. (2011). Antiproliferation and induction of apoptosis by *Moringa oleifera* leaf extract on human cancer cells. *Food and Chemical Toxicology*, 49(6), 1270–1275.

[59] Waterman, C., Cheng, D.M., Rojas-Silva, P., Poulev, A., Dreifus, J., Lila, M.A., & Raskin, I. (2014). Stable, water-extractable isothiocyanates from *Moringa oleifera* leaves attenuate inflammation in vitro. *Phytochemistry*, 103, 114–122.

[60] Jung, I.L. (2014). Soluble extract from *Moringa oleifera* leaves with a new anticancer activity. *PLoS ONE*, 9(4), e95492.

[61] Guon, T.E., & Chung, H.S. (2017). *Moringa oleifera* fruit induces apoptosis via ROS-dependent MAPK activation in human melanoma A2058 cells. *Oncology Letters*, 14(2), 1703–1710.

[62] Leelawat, S., & Leelawat, K. (2017). Molecular mechanisms of cholangiocarcinoma cell inhibition by medicinal plants. *Oncology Letters*, 13(2), 961–966.

[63] Khan, M., Yu, B., Rasul, A., Al, S.A., Yi, F., Yang, H., & Ma, T. (2012). Jaceosidin induces apoptosis in U87 glioblastoma cells through G2/M phase arrest. *Evidence-Based Complementary and Alternative Medicine*, 2012, 703034.

[64] Khan, M., Zheng, B., Yi, F., Rasul, A., Gu, Z., Li, T., Gao, H., Qazi, J.I., Yang, H., & Ma, T. (2012). Pseudolaric Acid B induces caspase-dependent and caspase-independent apoptosis in U87 glioblastoma cells. *Evidence-Based Complementary and Alternative Medicine*, 2012, 957568.

[65] Kou, X., Fan, J., & Chen, N. (2017). Potential molecular targets of ampelopsin in prevention and treatment of cancers. *Anti-Cancer Agents in Medicinal Chemistry*, 17(12), 1610–1616.

[66] Jafarain, A., Asghari, G., & Ghassami, E. (2014). Evaluation of cytotoxicity of *Moringa oleifera* Lam. callus and leaf extracts on HeLa cells. *Advanced Biomedical Research*, 3,

[67] Singh, R.P., Padmavathi, B., & Rao, A.R. (2000). Modulatory influence of *Justicia adhatoda* leaf extract on xenobiotic metabolism enzymes and antioxidant status. *Molecular and Cellular Biochemistry*, 213(1–2), 99–109.

[68] Sharma, V., Paliwal, R., Janmeda, P., & Sharma, S. (2012). Chemopreventive efficacy of *Moringa oleifera* pods against DMBA-induced hepatic carcinogenesis in mice. *Asian Pacific Journal of Cancer Prevention*, 13(6), 2563–2569.

[69] Bharali, R., Tabassum, J., & Azad, M.R. (2003). Chemomodulatory effect of *Moringa oleifera* on hepatic carcinogen metabolizing enzymes and antioxidant parameters. *Asian Pacific Journal of Cancer Prevention*, 4(2), 131–139.

[70] Sharma, V., & Paliwal, R. (2014). Potential chemoprevention of DMBA-induced renal carcinogenesis by *Moringa oleifera* pods and its isolated saponin. *Indian Journal of Clinical Biochemistry*, 29(2), 202–209.

[71] Grover, J.K., Yadav, S., & Vats, V. (2002). Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology*, 81(1), 81–100.

[72] Kar, A., Choudhary, B.K., & Bandyopadhyay, N.G. (2003). Comparative evaluation of hypoglycemic activity of some Indian medicinal plants. *Journal of Ethnopharmacology*, 84(1), 105–108.

[73] Mbikay, M. (2012). Therapeutic potential of *Moringa oleifera* leaves in chronic hyperglycemia and dyslipidemia: A review. *Frontiers in Pharmacology*, 3, 24.

[74] Omabe, M., Nwudele, C., Omabe, K.N., & Okorocha, A.E. (2014). Anion gap toxicity in alloxan-induced type 2 diabetic rats treated with *Moringa oleifera* extract. *Journal of Toxicology*, 2014, 406242.

[75] Tuorkey, M.J. (2016). Effects of *Moringa oleifera* aqueous leaf extract in alloxan-induced diabetic mice. *Interventional Medicine & Applied Science*, 8(3), 109–117.

[76] Ndong, M., Uehara, M., Katsumata, S., & Suzuki, K. (2007). Effects of oral administration of *Moringa oleifera* Lam. on glucose tolerance in Goto-Kakizaki and Wistar rats. *Journal of Clinical Biochemistry and Nutrition*, 40(3), 229–233.

[77] Omodanisi, E.I., Aboua, Y.G., & Oguntibeju, O.O. (2017). Assessment of the anti-hyperglycaemic and anti-inflammatory activities

of *Moringa oleifera* in a diabetic rat model. *Molecules*, 22(6), 872.

[78] Adedapo, A.A., Mogbojuri, O.M., & Emikpe, B.O. (2009). Safety evaluations of the aqueous extract of the leaves of *Moringa oleifera* in rats. *Journal of Medicinal Plants Research*, 3(8), 586–591.

[79] Mizushima, N., & Komatsu, M. (2011). Autophagy: Renovation of cells and tissues. *Cell*, 147(4), 728–741.

[80] Levine, B., & Kroemer, G. (2008). Autophagy in the pathogenesis of disease. *Cell*, 132(1), 27–42.

[81] Deretic, V., Saitoh, T., & Akira, S. (2013). Autophagy in infection, inflammation and immunity. *Nature Reviews Immunology*, 13(10), 722–737.

[82] Rubinsztein, D.C., Mariño, G., & Kroemer, G. (2011). Autophagy and aging. *Cell*, 146(5), 682–695.

[83] White, E., Mehnert, J.M., & Chan, C.S. (2015). Autophagy, metabolism, and cancer. *Clinical Cancer Research*, 21(22), 5037–5046.

[84] Li, J., & Yuan, J. (2008). Caspases in apoptosis and beyond. *Oncogene*, 27(48), 6194–6206.