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Moringa oleifera Lam.: a comprehensive review on active components, health benefits and application†

Xinyue Su,‡[a] Guanzheng Lu,‡[a] Liang Ye,[a] Ruyu Shi,[a] Maomao Zhu,[a] Xinming Yu,[a] Zhiyong Li,*[b] Xiaobin Jia*[a] and Liang Feng *[a]

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Moringa oleifera Lam. is an edible therapeutic plant that is native to India and widely cultivated in tropical countries. In this paper, the current application of *M. oleifera* was discussed by summarizing its medicinal parts, active components and potential mechanism. The emerging products of various formats such as drug preparation and product application reported in the last years were also clarified. Based on literature reports, the unique components and biological activities of *M. oleifera* need to be further studied. In the future, a variety of new technologies should be applied to the development of *M. oleifera* products, to enrich the varieties of dosage forms, improve the bitter taste masking technology, and make it better for use in the fields of food and medicine.

Introduction

Moringa oleifera Lam. (*M. oleifera*), also known as drumstick or horseradish, is a perennial tree that belongs to the Moringaceae family.[1] It is considered to be a medicine food homology plant with great medicinal values and was introduced into Yunnan province, China, in the 1960.[2] *M. oleifera*, acquainted with "Tree of Wonders", "Tree of Life" and "Diamond of Plants", is widely cultivated for its drought resistance, rapid growth and nutrient-rich properties in African and Asian countries.[3] (Fig. 1). *M. oleifera* is a remarkable plant with multiple edible parts, each offering unique biological activities. Its leaves, fruit pods, fruits, seeds, flowers, and roots all contribute to its versatility and potential benefits. And in India and Africa, it is commonly used to treat diabetes, skin diseases, hypoimmunity, arthritis, cancer, and so on.

The safety of *M. oleifera* is closely related to its ingredients, therefore, an increasing number of scholars have focused on the identification of the active compounds for the investigation of its pharmacological effects and potential mechanisms which are crucial in the process of *M. oleifera* application of drugs and food products development. It is of great significance and value to explore the relationship between its ingredients and efficacy, the determination of key ingredients, the selection of different dosage forms and the toxicity evaluation of *M. oleifera* on the human body. Fortunately, studies on *M. oleifera* have been conducted and numerous new active ingredients were found, leading to the developments of new preparation methods, pharmacological efficacies and toxicological effects of *M. oleifera*. What's more, the underlying molecular mechanism of *M. oleifera* action is also being revealed.[4]

This article summarized the past 10 years of research on the medicinal parts, active ingredients, health benefits and the mechanisms, dosage forms and applications of *M. oleifera*. In addition, we also use UPLC-Q-TOF-MS, network pharmacology and molecular docking to analyse the components and pharmacological mechanisms. This article summarizes and explains the chemical composition and biological activity and mechanisms of action of *M. oleifera*. It predicts trends in the expansion of *M. oleifera* products and formulation design with a focus on innovation and diversification, aiming to provide theoretical support and research ideas for subsequent studies. In this way, this paper provides not only a basic research summary but also a comprehensive future research plan for *M. oleifera*. Furthermore, the challenges and future trends of *M. oleifera* are summarized to provide a research approach for the further development and application.

M. oleifera related article acquisition based on CiteSpace

This study regards the Web of Science Core Collection as a data-collection platform according to data resources required in CiteSpace. The bibliometric search strategy can be described as the following: topics = ("*Moringa oleifera* Lam. OR *Moringa*

[a]*School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing 211198, P. R. China. E-mail: jiaxiaobin2015@163.com; wenmoxiushi@163.com*

[b]*Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, P. R. China. E-mail: lizhiyong7899@sina.com*

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‡ These authors contributed equally to this work.

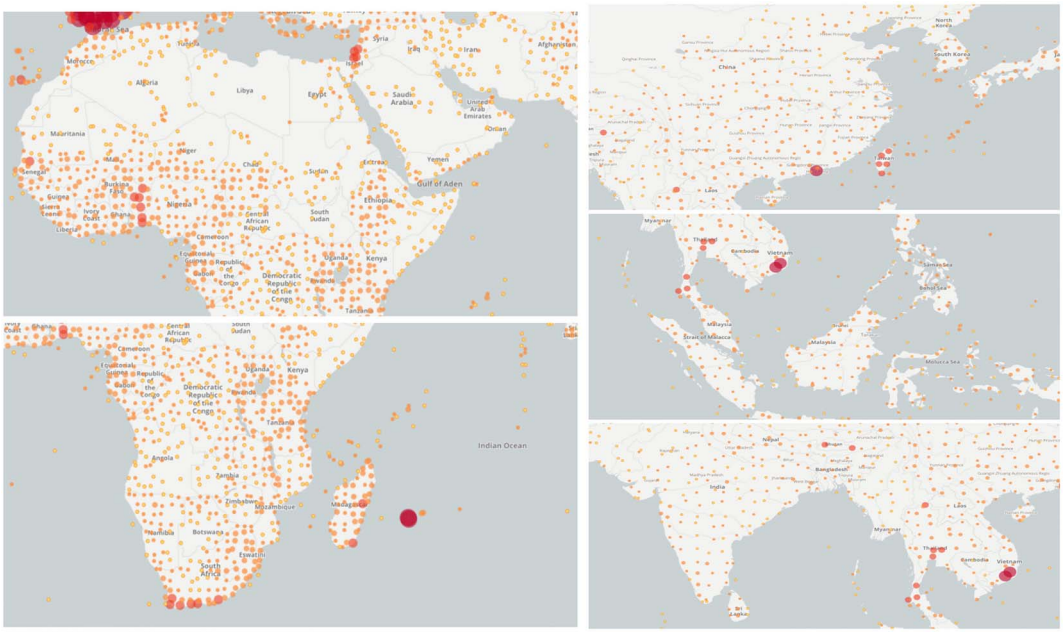

Fig. 1 Key distribution areas of *M. oleifera* worldwide (the dots indicate the presence of *M. oleifera* in this area. Images were obtained from https://www.gbif.org/).

oleifera OR Moringa"), time span = 2012–2023, and language = English.[5] We used the 6.1.R6 version of CiteSpace software to analyse the current hot spots of *M. oleifera*.

We searched 5249 publications related to *M. oleifera*. (Fig. 2A) Bergamasco Rosangela was the most prolific author with most publications, *i.e.*, with 60 articles (Fig. 2B). The India, Egypt and China were the leading country and the top institution in this field of study, with 725, 372 and 348 articles, respectively (Fig. 2C). There was active cooperation between institutions, countries, and authors. Hot topics focused on

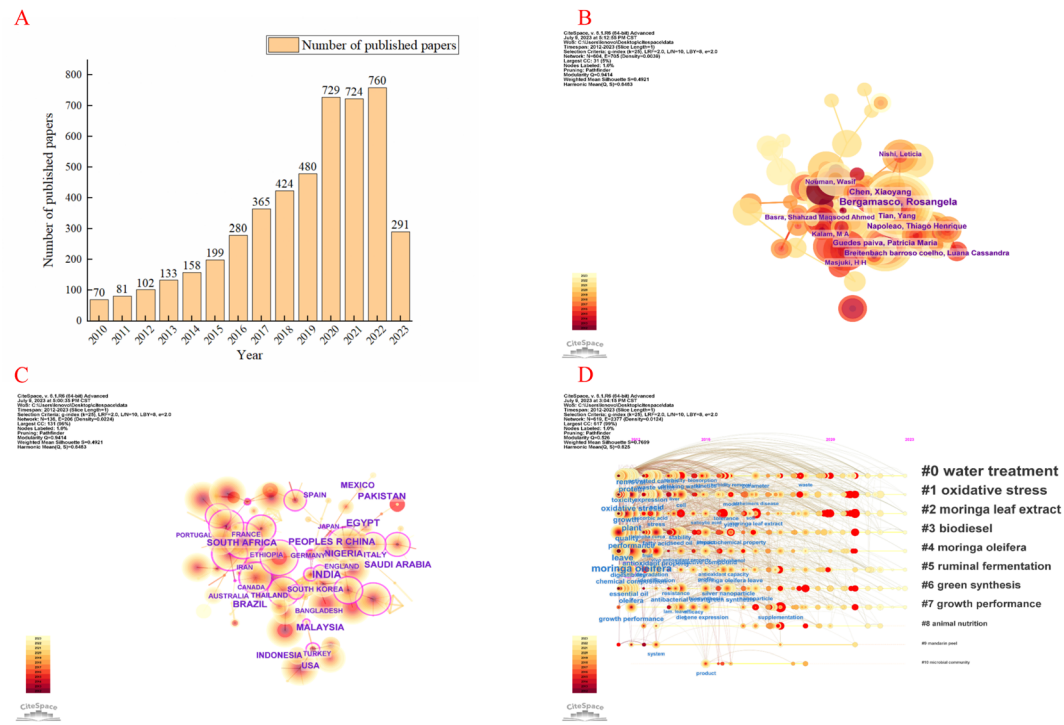

Fig. 2 CiteSpace, the Java application, can be used to generate knowledge-domain visualization. Annual trend chart of publications (A). The network of author and countries in the study area of insomnia and circadian rhythm (B and C). Timeline diagram of keywords in the field of *M. oleifera* (D).

Moringa oleifera leave, *Moringa oleifera* extract, antioxidant activity, and oxidative stress (Fig. 2D).

Medicinal parts of *M. oleifera*

The whole plant of *M. oleifera* including leaf, fruit pod, fruit, seed, flower and root, all have a variety of biological activities, and can even play medicinal roles in preventing and treating diseases.

The leaves of *M. oleifera* are rich in resources and easily harvested which mainly contain active components such as polyphenols, flavonoids, phenylpropanoids, terpenoids, fatty acids, alkanes, sterols, as well as minerals and vitamins.[6] Among them, polyphenols and flavonoids are the main bioactive constituents, with antioxidant activity and anticancer properties,[7] antisepsis,[8] anti-inflammatory,[9] anti-hypertension, anti-diabetes, anti-spasm, reduce metal toxicity,[10] reduces plasma and liver lipids and affects obesity-related reproductive

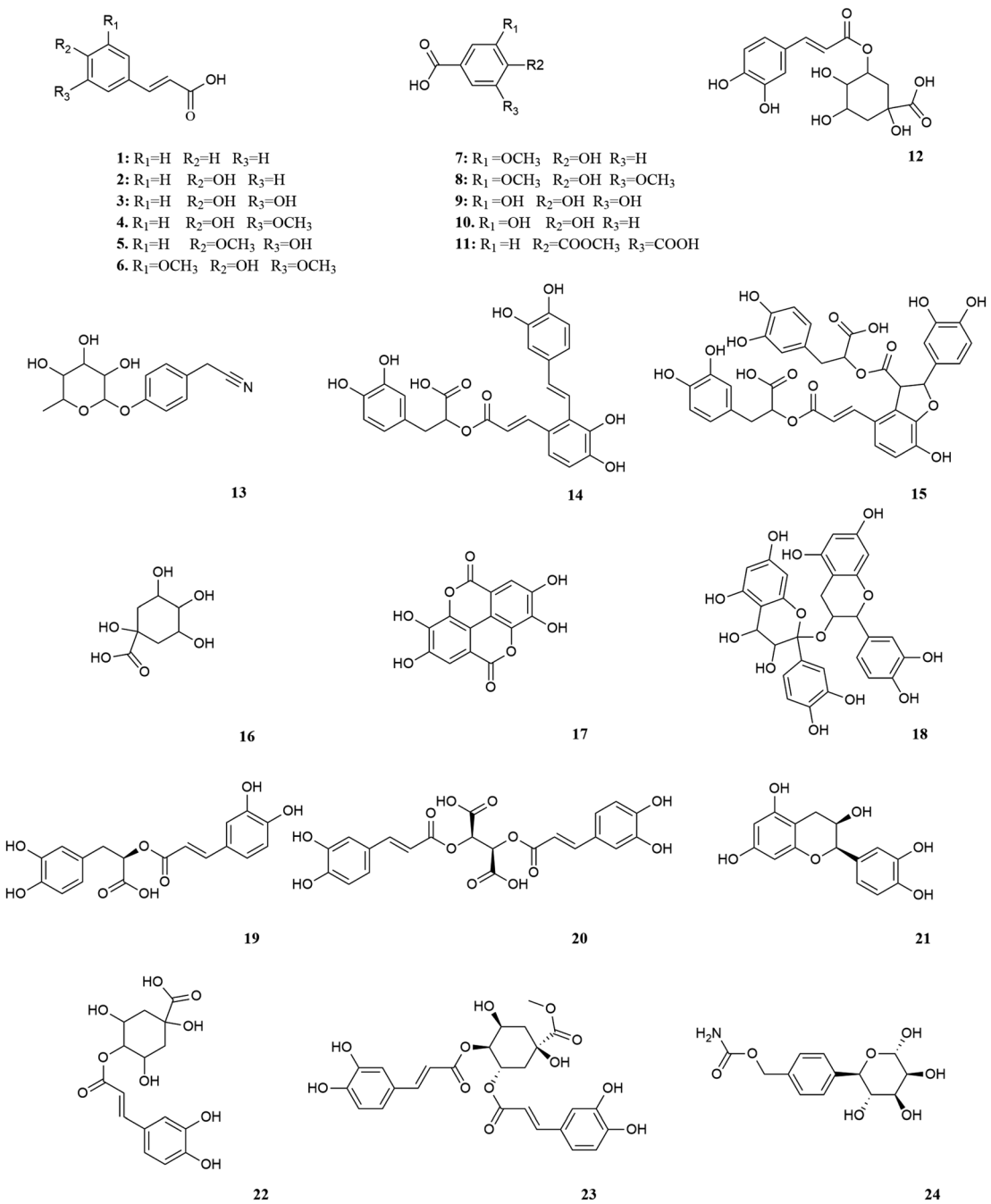

Fig. 3 Polyphenols in *M. oleifera*. [1] Cinnamic acid, [2] *p*-coumaric acid, [3] caffeic acid, [4] ferulic acid, [5] isoferic acid, [6] sinapic acid, [7] vanillic acid, [8] syringic acid, [9] gallic acid, [10] protocatechuic acid, [11] gentiolic acid, [12] chlorogenic acid, [13] niazirin, [14] salvianolic acid A, [15] salvianolic acid B, [16] quinic acid, [17] ellagic acid, [18] procyanidin, [19] rosmarinic acid, [20] chicoric acid, [21] epicatechin, [22] 4-*O*-caffeoylqunic acid, [23] 3,4-di-*O*-caffeoylquinic, [24] 4-methyl-(α-L-rhamnose pyranoxy)-carbamate.

diseases[11] and anti-epilepsy,[9] affect reproductive diseases[12] and other activities.

The seeds of *M. oleifera* are mainly composed of protein, fatty and flavonoids, and essential amino acids required by the human body.[13–15] Furthermore, the isothiocyanates contained in *M. oleifera* seeds also play a crucial role in anti-inflammatory, antioxidant, antibacterial and anticancer.[16] And the essential oil has coagulant effect that can accelerate wound healing.[17]

While previous research on *M. oleifera* mainly focused on the leaves and seeds, there has been limited discourse on its stems. Methanol reflux method and column tomography were used to extract four compounds, namely cholest-5-en-3-ol, stigmasterol,

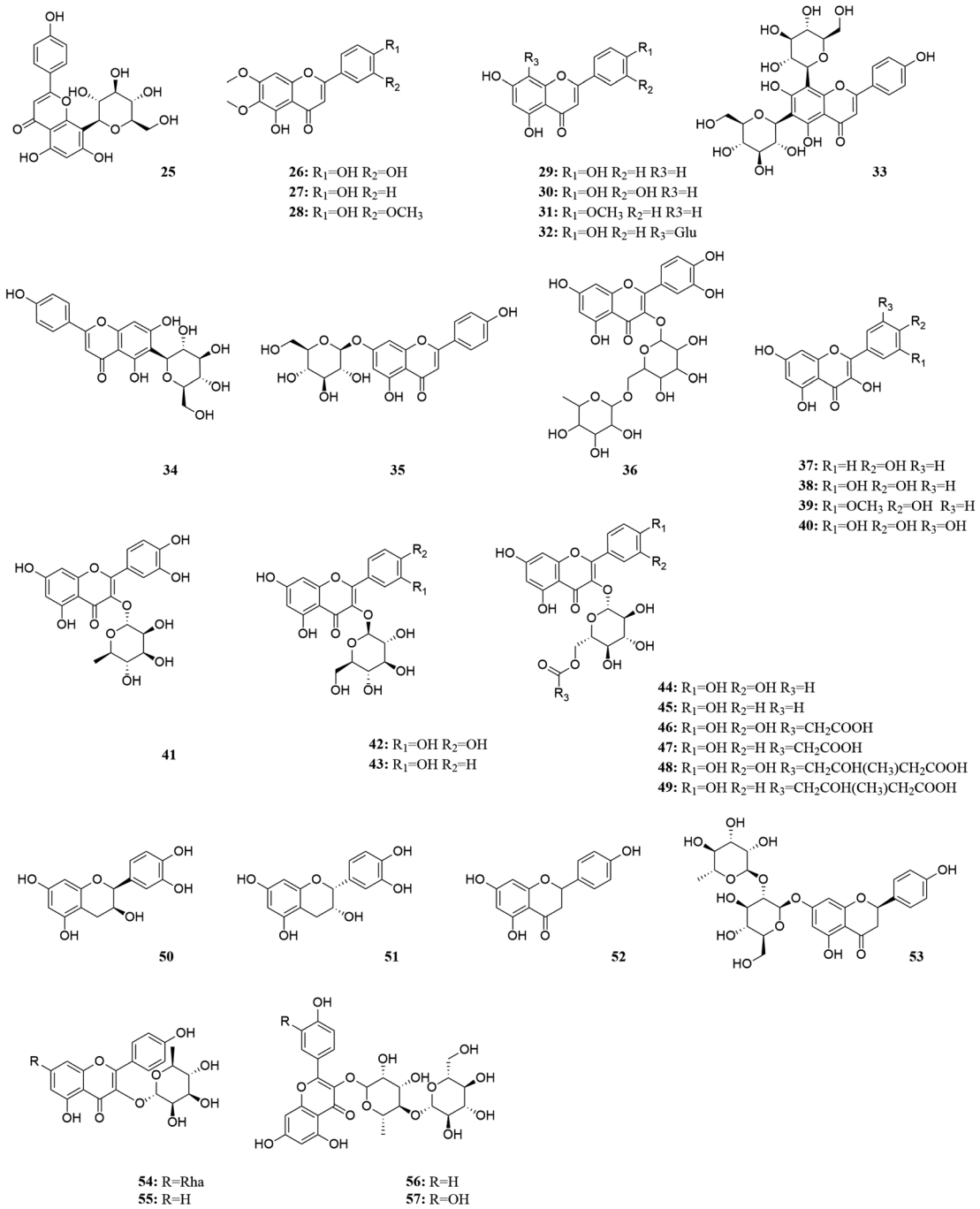

Fig. 4 Flavonoids in *M. oleifera*. [25] Vitexin, [26] cirsiliol, [27] cirsimaritin, [28] cirsilineol, [29] apigenin, [30] luteolin, [31] acacetin, [32] vitexin, [33] vicenin 2, [34] isovitexin, [35] cosmosiin, [36] rutin, [37] kaempferol, [38] quercetin, [39] isorhamnetin, [40] myricetin, [41] quercitrin, [42] isoquercitrin, [43] astragalin, [44] quercetin-3-*O*-(6″-acetyl-glucoside), [45] kaempferol-3-*O*-(6″-acetyl glucoside), [46] quercetin-3-*O*-(6-malondiyl)-β-D-glucopyranoside, [47] kaempferol-3-*O*-malondiacylhexanoside, [48] quercetin-3-*O*-hydroxymethyl glutaryl galactoside, [49] kaempferol-3-*O*-hydroxymethyl glutaryl hexanoside, [50] catechin, [51] (−)-epicatechin, [52] naringenin, [53] naringin, [54] kaempferitrin, [55] myricitrin, [56] multiflorin-B, [57] multinoside A.

gamma-sitosterol, and tricosanoic acid, from the stem of *M. oleifera*. These fractions and the methanol extract showed strong antifungal activity against *Rhizoctonia solani* and *Fusarium oxysporum*.[18] The resulting fractions derived from different solvents such as hexane, benzene, chloroform, ethyl acetate, acetone and water have been found to have activities against *Rhizoctonia solani* and *Fusarium oxysporum*. *M. oleifera* flowers and fruits are rich in carbohydrates, proteins, organic acids, flavonoids and phenols. Singhal *et al.* recorded that tocopherols, ascorbic acid, carotenoids and flavonoids, are antioxidants and have the ability to eliminate reactive oxygen species (ROS).[19]

Chemical components of *M. oleifera*

M. oleifera contains a variety of functional active ingredients, which underlie its use as a dietary supplement and functional food. The reported functional active ingredients and their specific effects in *M. oleifera* are summarized through comprehensive literature review by ChemDraw 19.0 (Fig. 3–8, Table 1).

According to research conducted by Tekayev *et al.* (2010) and Tesfaye *et al.* (2022), moringa leaves, flowers, seeds, and other nutritional parts are plentiful in multiple nutrients and can be utilized as both food and medicine.[20,21] In order to further explore and analyze the functional components and mechanism of the main nutrient parts of *M. oleifera*, the dry leaves and seeds (MOL and MOS) of *M. oleifera* were analysed by UPLC-Q-TOF-MS. Manual calibration was performed to verify the accurate mass-to-charge ratio, secondary fragment ion information and literature data for each compound, identifying 33 MOL and 45 MOS components, respectively. Under the proposed analysis conditions, the total ion flow diagram of *M. oleifera* in positive and negative ion mode are shown in Fig. 9.

The compound of MOL includes 13 flavonoids, 5 phenolic acids, 6 amino acids, 3 phenylpropanoids, 2 phytosterols, 2 terpenoids (2 triterpenoid saponins) and 2 vitamins which are detailed in Table 2. The information of MOS obtained by identification is shown in the table below and includes 19 flavonoids, 11 phenolic acids, 5 amino acids, 7 phenylpropanoids, 1 terpenoid (1 triterpenoid saponin), 2 vitamins.

Toxicity of *M. oleifera*

M. oleifera leaf extracts were tested by WST-1 assay with melanoma cells (A375 human malignant melanoma cell line, A2058 human metastatic melanoma cell line) and normal human dermal fibroblasts (NHDF, WS1).[7] The results showed that *M. oleifera* extract could inhibit the proliferation of both melanoma cells in a dose-dependent manner. However, *M. oleifera* extract had no significant inhibitory effect on both normal human somatic cells (IC50 > 200 μg mL^{-1}), even at the highest concentration (200 μg mL^{-1}), showed only mild cytotoxicity to normal cells after 48 h.

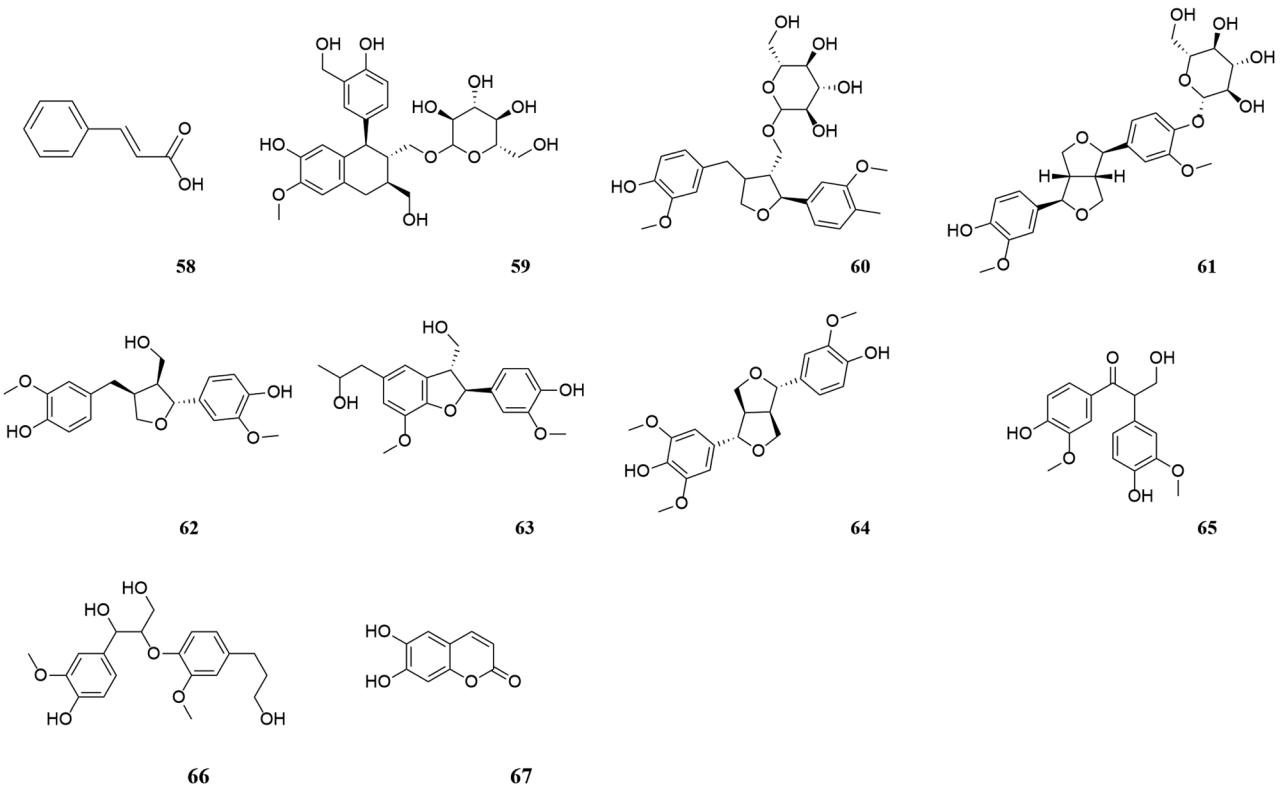

Fig. 5 Phenylpropanoids in *M. oleifera*. **[58]** Cinnamic acid, **[59]** (+)-isolariciresinol-3a-*O*-β-D-glucopyranoside, **[60]** lariciresinol-9-*O*-β-D-glucopyranoside, **[61]** (+)-pi-noresinol-4-*O*-β-D-glucopyranoside, **[62]** lariciresinol, **[63]** (7*S*,8*R*)-dihydrodehydrodiguaiacyl alcohol, **[64]** medioresinol, **[65]** evofolin B, **[66]** 1-(4-hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxypropyl)-2, **[67]** esculetin.

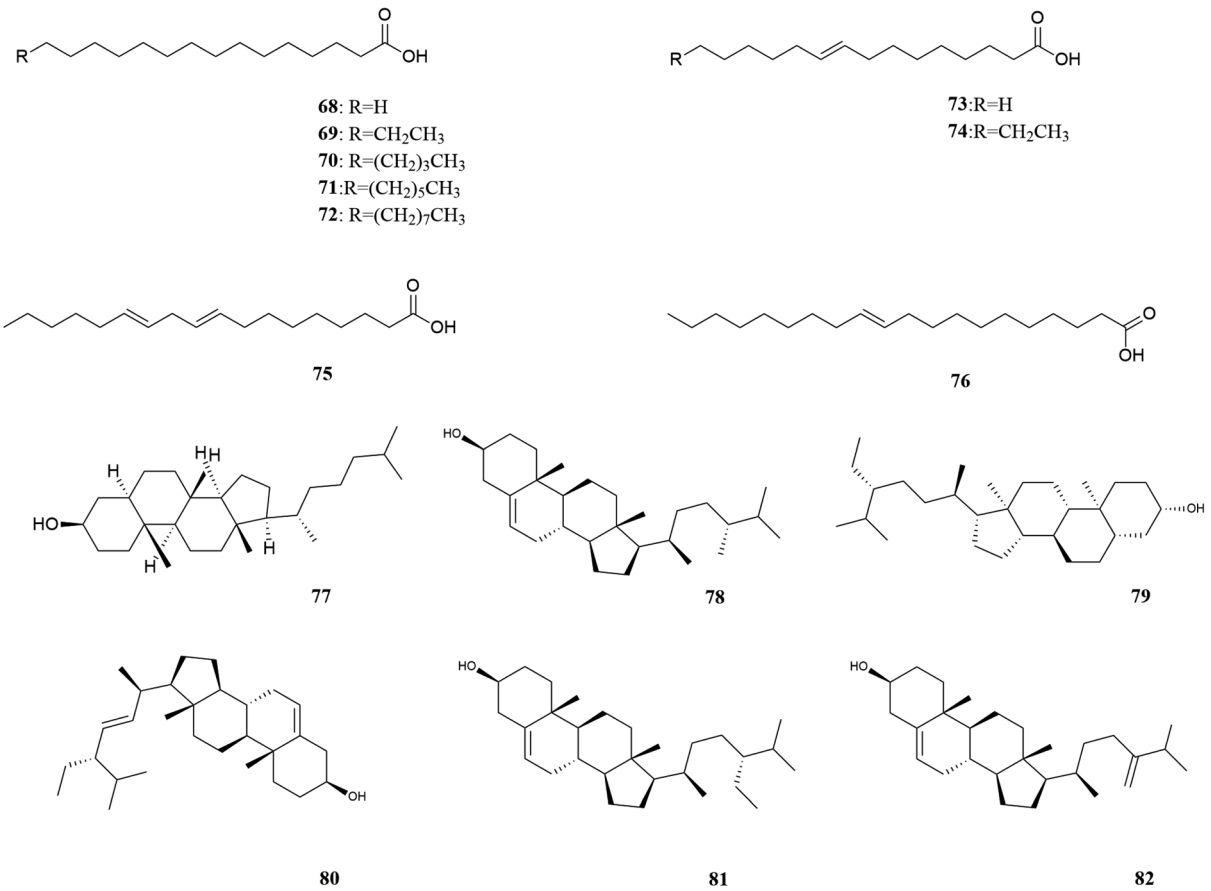

Fig. 6 Fatty acids and plant sterols in *M. oleifera*. [68] Palmitic acid, [69] palmitoleic acid, [70] arachidic acid, [71] behenic acid, [72] lignoceric acid, [73] stearic acid, [74] oleic acid, [75] linoleic Acid, [76] eicosenoic acid [77] 5α-cholestan-3β-ol, [78] campesterol, [79] stigmastanol, [80] stigmasterol, [81] β-sitosterol, [82] 24-methylenecholesterol.

The subacute and acute (5000 mg kg^{-1}) toxic effects of the extract of *M. oleifera* (40–1000 mg kg^{-1}) on rats were studied. It has been shown that the extract is reasonably safe for consumption.[22] Siddiqui *et al.* studied the cytotoxicity of *M. oleifera* fruits to human liver cancer, and analysed the risk parameters of mutagenicity, tumgenesis, reproductive and irritability as well as drug toxicity of *M. oleifera* fruits.[23] The results showed that there was no predictive toxicity of the drug candidates, indicating that *M. oleifera* fruit extract is a safe and potential anticancer drug. The potential of silver nanocomposites (MOS-PS-AGNPs) with *M. oleifera* seed polysaccharides as an alternative dressing was prepared and investigated. The cytotoxicity of the nanocomposites *in vitro* was also investigated using mouse fibroblasts (L929). The results showed that MOS-PS-AGNPs of 0–200 μg mL^{-1} had no obvious cytotoxicity to L929, at higher concentrations (200 μg mL^{-1}), MOS-PS-AGNPs showed slight cytotoxicity and was negligible. In summary, MOS-Ps-AGNPs was non-toxic to fibroblast L929.[24]

Although *M. oleifera* and its extracts have been proved to be safe *in vivo* and *in vitro*, some studies have shown that *M. oleifera* may have potential reproductive toxicity. The findings suggest that the methanol seed extract of *Moringa stenopetala* is not safe to rat embryos and fetuses. Its toxic effects were evidenced by a significant delay in embryonic and fetal development and an increase in fetal resorptions and fetal death.[25] The contraceptive ability and uterine activity of water extract of *M. oleifera* leaf extract were investigated *in vivo* and *in vitro*. It was found that water extract could prevent pregnancy, induce abortion and myometrial contraction in rats.[26] Hence, *M. oleifera* are quite safe when used under the certain dose range, and more attention should be paid to their use in special target audiences.

Health benefits of *M. oleifera*

Although *M. oleifera* is commonly used as a functional food, its pharmacological action is non-negligible. It is capable of preventing or treating diseases such as lung cancer,[4] breast carcinoma,[92] diabetes,[93] periodontitis,[94] acute pancreatitis[95] and the others. The compounds mentioned above in *M. oleifera* contribute to the antioxidant, anti-inflammatory, anti-cancer, antibacterial and antiviral activities. Next, we will summarize the functions in detail (Table 3).

Antioxidant and anti-inflammatory effect

The oxidative stress derives from the imbalance between the generation of ROS and antioxidant system, commonly leading

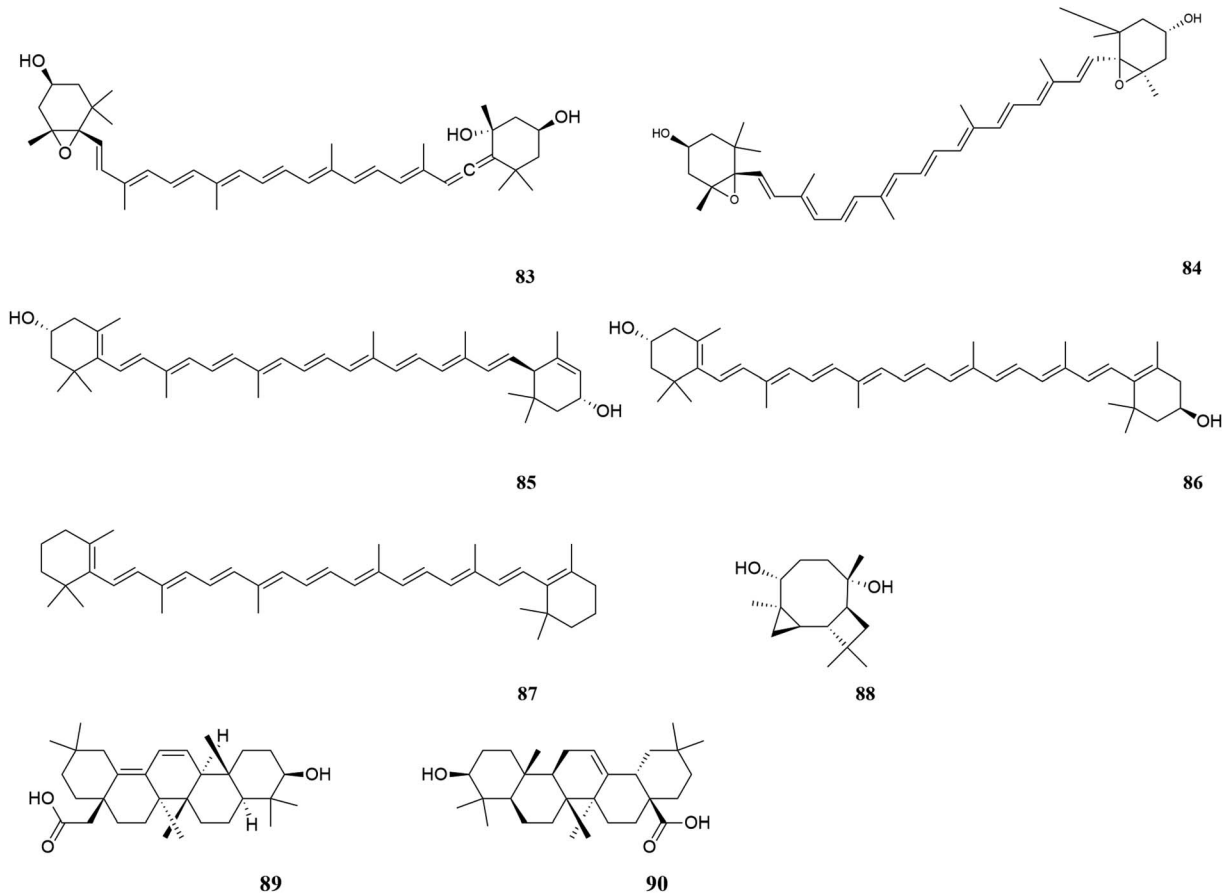

Fig. 7 Terpenoids in *M. oleifera*. **[83]** Neoxanthin, **[84]** violaxanthin, **[85]** lutein, **[86]** zeaxanthin, **[87]** β-carotene, **[88]** tricyclohumuladiol, **[89]** 3β-hydroxy-oleano-11,13(18)-diene-28-carboxylic acid, **[90]** oleanolic acid.

to inflammation and consequently to a variety of diseases such as pancreatitis,[96] periodontitis,[97] arthritis,[98] acute kidney injury,[99] colitis[100] and so on. Previous studies have suggested that the flavonoids and polyphenols contained in *M. oleifera*, such as rutin and myricetin, are the main active ingredients that exert the antioxidant and anti-inflammatory functions.[101] In

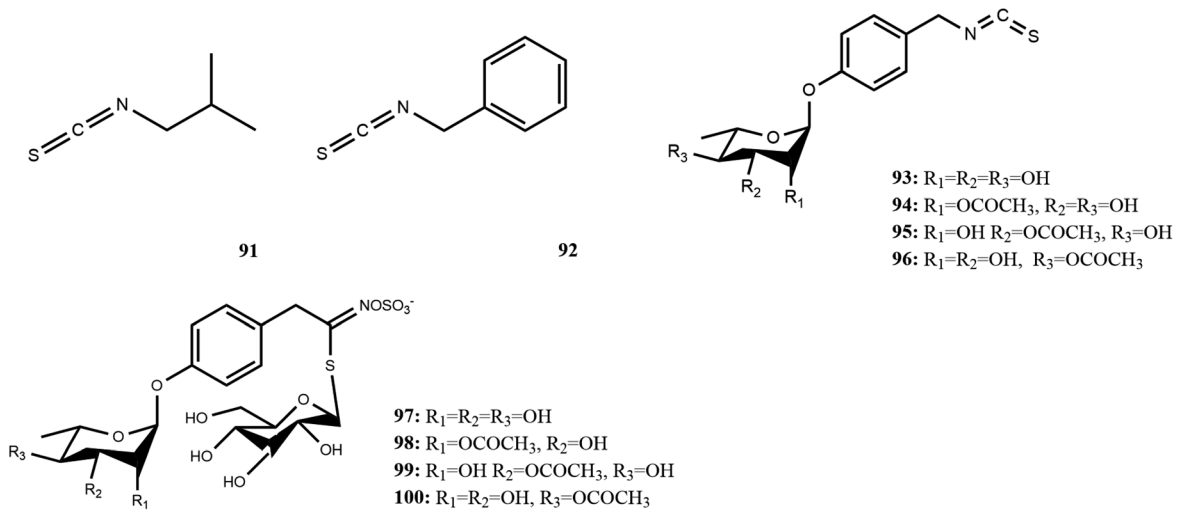

Fig. 8 Glucosinolates and isothiocyanate in *M. oleifera*. **[91]** isobutyl isothiocyanate, **[92]** benzyl isothiocyanate, **[93]** 4-[(α-L-rhamnosyloxy) benzyl] isothiocyanate, **[94]** 4-[(2-*O*-acetyl-α-L-rhamnosyloxy) benzyl] isothiocyanate, **[95]** 4-[(3-*O*-acetyl-α-L-rhamnosyloxy) benzyl]isothiocyanate, **[96]** 4-[(4-*O*-acetyl-α-L-rhamnosyloxy)benzyl] isothiocyanate, **[97]** 4-[(α-L-rhamnosyloxy)benzyl]glucosinolate, **[98]** 4-[(2′-*O*-acetyl-α-L-rhamnosyloxy) benzyl]glucosinolate, **[99]** 4-[(3′-*O*-acetyl-α-L-rhamnosyloxy)benzyl] glucosinolate, **[100]** 4-[(4′-*O*-acetyl-α-L-rhamnosyloxy) benzyl]glucosinolate.

Table 1 Bioactivities of the main components extracted from *M. oleifera*

Number	Components	Bioactivities	Diseases/tissues	Effects and function	Ref.
1	Polyphenols	Antioxidant	Hypertension/ neurodegeneration	Free radical scavenging activities	27 and 28
				Inhibition of free radical, lipid peroxidation, cholinergic and monoaminergic activity	29
			Diabetes	Inhibition of α-amylase activity	30 and 31
			Enhance sexual function and the male reproductive system	Scavenged DPPH radical, ABTS radical and H_2O_2 and suppressed the formation of LPO and AGEs	32
			Anti-aging	Reduce lipid peroxidation and lipofuscin pigmentation and increase serotonin and antioxidant enzymes in the brain of aged rats	33
			Other		27 and 34
		Anticancer		Caspase-dependent and caspase-independent apoptotic pathways mediated by mitochondrial ROS are involved	35
		Metabolic syndrome	Improve hyperglycemia, insulin resistance, inflammation, carbohydrate and lipid metabolism, non-alcoholic fatty liver	Reduce food intake, water intake and body weight, lower blood glucose levels and improve inflammation	1 and 9
1	Polyphenols	Antibacterial	*S. aureus*, *Bacillus cereus*	Bacterial cell damage and leakage of intracellular substances	36 and 37
		Anti-inflammatory	Arthritis	Scavenging of free radicals, inhibition of protein denaturation, membrane stabilization and anti-proteinase activity	6, 9 and 38
2	Flavonoids	Anticancer/cytotoxic activity	Cancer (colon cancer, lung cancer)	By working directly on visceral mass and restoring mRNA expression of leptin, resistin, and adiponectin genes	27
		Antioxidant	Hypolipidemic effects	Improve body weight, atherogenic index and insulin resistance in obese rats	30
			Diabetes	Induced insulin secretion	30 and 31
			Myocardial damage	Decreased the apoptotic markers Bax, cytochrome-c and iNOS expression, induced NO level, and increased BCl_2 markers	30
			Reduce metal toxicity	Protect yeast cells against As(III) toxicity, likely through its role in decreasing As(III) accumulation and As(III)-induced ROS production, the hydroxyl and carboxyl groups of gallic acid appear to play a critical role in chelating As(III) inhibition of the accumulation of toxic metals in the body	
2	Flavonoids	Antihypertensive effects	Hypertension	ACE inhibition test showed ACE inhibition activity	30
			Enhance sexual function and the male reproductive system	Enhanced courtship behavior and reproductive function	12
		Antiviral	COVID-19	High docking binding affinity for non-structural proteins nsp9 and nsp10 of COVID-19	39

Table 1 (*Contd.*)

Number	Components	Bioactivities	Diseases/tissues	Effects and function	Ref.
2	Flavonoids	Regulate intestinal flora		Regulate the proportion of digestive tract flora	40
		Promote the proliferation and migration of fibroblasts	Promote wound healing	Induced fibroblast proliferation and cell migration	41
3	Fatty acids and plant sterols	Antioxidant	Hypolipidemic effects	Improved body weight, total cholesterol, triglyceride and LDL levels in obese rats	30 and 42
		Anticancer		Apoptotic cells can be significantly induced by changing mitochondrial membrane potential in EAC cell lines	43
4	Glucosinolates and isothiocyanate	Antihypertensive effects	Hypertension	Reduce vascular oxidation in spontaneously hypertensive rats	30
		Anticancer	MCF-7, HepG2 and HCT-116	Inhibition of IL-3 – induced STAT5 target gene expression. The isothiocyanate group of moringin should be necessary for its chemoprotective activities	42, 44 and 45
		Antioxidant	Diabetes	Lower body weight, reduce obesity, improve glucose tolerance, reduce inflammatory gene expression, increase antioxidant gene expression improved glucose tolerance and reduced obesity, inflammation and oxidative stress. Antibiotic-like recombination regulates the gut microbiome	46
		Anti-inflammatory			
		Antioxidant	Skin photoaging	It is beneficial to the uptake of HaCaT cells, thus improving the activity of antioxidant enzymes, clearing UVB-induced ROS, protecting skin from damage, and reducing the expression of MMP-1, MMP-3 and MMP-9 caused by radiation-induced photoaging	16
		Antibacterial	*L. monocytogenes*	Damage the integrity of cell walls and membranes, stimulate oxidative stress, interfere with energy metabolism and DNA replication	47
5	Polysaccharides	Antioxidant		DPPH radical scavenging activity removes excess free radicals from the system and protects them from oxidative damage	48–51
		Antidiabetic		α-Amylase inhibition and α-glucosidase inhibition	
		Regulate intestinal flora		Increased villus height and mucosal thickness in the ileum, colon, and duodenum, as well as villus height and crypt depth ratio in the ileum. Boost the activity of digestive enzymes. Improved the variety of the gut microbiota in mice	48, 51 and 52
		Hypolipemia	Hyperlipidaemia	Effective bile acid sequestrants	53
		Immunomodulatory effect		Enhanced pinocytic rate and increased production of ROS, NO, IL-6, and TNF-α levels	48, 51 and 54
		Anti-inflammatory	Rheumatoid arthriti, inflammatory bowel disease, asthma, and pancreatitis	Inhibited the production of IL-6 and TNF-α	51
		Anticancer	Human ovarian cancer	Induce apoptosis of cancer cells and suppress cancer cell proliferation	49
		Antibacterial	Wound healing	Promote wound contraction and internal tissue growth. It has highly potent and durable antibacterial activity against infectious pathogens in wounds	24

Table 1 (*Contd.*)

Number	Components	Bioactivities	Diseases/tissues	Effects and function	Ref.
6	Others	Antibacterial	*S. aureus*	Irreversible membrane damage is caused to *S. aureus* cells by increasing membrane permeability, leading to the release of intracellular nucleotide pools	55
		Anti-inflammatory		Inhibit DPPH and ABTS free radicals, and inhibit the production of NO	56
		Antioxidant			
		Antihypertensive effects	Hypertension	Reduction in systolic and diastolic blood pressure in spontaneously hypertensive rats	57
6	Others	Antibacterial	H1N1 virus	Inhibition of virus replication in host cells has a protective effect on infected cytopathies caused by IAVS	58 and 59

addition, isothiocyanates, which are abundant in the seeds of *M. oleifera*, also exhibit these effects both *in vitro* and *in vivo*.[63] The specific mechanism of the anti-inflammatory effect of MO may be through regulating the gene expression levels of inflammatory cytokines. These cytokines include interleukin-6 (IL-6), interleukin-17A (IL-17A), interleukin-4 (IL-4), interleukin-10 (IL-10), nitric oxide (NO), inducible nitric oxide synthase (iNOS) and interleukin-1β (IL-1β). In addition, the gene expression of antioxidant factor (quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX) and antioxidant enzyme (GSTP1)) is regulated to play the role of antioxidant (Fig. 10).

Antitumor effect

Cancer remains a major health concern with chemotherapy previously prescribed having significant side effects. The plant-based therapies have become a hot research topic in recent years. *M. oleifera* contains a variety of bioactive substances that have positive effects on the treatment for cancer.

M. oleifera leaves can fight against variety classes cancer cells. *M. oleifera* leaves water extract (MOE) has significant anticancer effect on melanoma cells *in vitro*, while it has almost no effect on normal human fibroblasts. The specific mechanisms of action involve mitochondrial-mediated Cleaved-Caspase and Caspase apoptosis pathway, indicating its potential for skin cancer treatment.[102]

Alkaloids, which are nitrogen-containing organic compounds, have demonstrated antitumor effects. *M. oleifera* alkaloids have been shown to inhibit PC3 cell proliferation and migration by inhibiting cyclooxygenase-2-mediated (COX-2-mediated) Wnt/β-catenin signaling pathway through *in vivo* and *in vitro* experiments. Lung cancer is one of the common malignant tumors. Studies have found that *M. oleifera* alkaloids also have therapeutic effects on lung cancer. Further experiment showed that *M. oleifera* can inhibit the proliferation and migration of human non small cell lung cancer cell (A549) cells by inhibiting the mechanisms related to activation of Janus kinase2/Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) pathway, and induce cell apoptosis and cell cycle arrest, further highlighting its potential in preventing and treating lung cancer.[4]

Improve gut microbiota effect

The importance of gut microbiota in human health has been revealed by numerous studies in recent years. The imbalance of intestinal flora is associated with some diseases, such as diabetes, obesity, chronic kidney disease and colitis. *M. oleifera* seed extract (MSE) was given to male C57BL/6J mice for 16S of fecal/cecum samples after 12 weeks of feeding together with normal diet and high-fat diet rRNA gene sequencing and quantitative Polymerase Chain Reaction (PCR) showed major changes in intestinal microbiota and significant reduction of bacterial load, similar to antibiotic response, suggesting that *M. oleifera* seed extract can improve metabolic health through antibiotic-like recombination of intestinal microbiota,

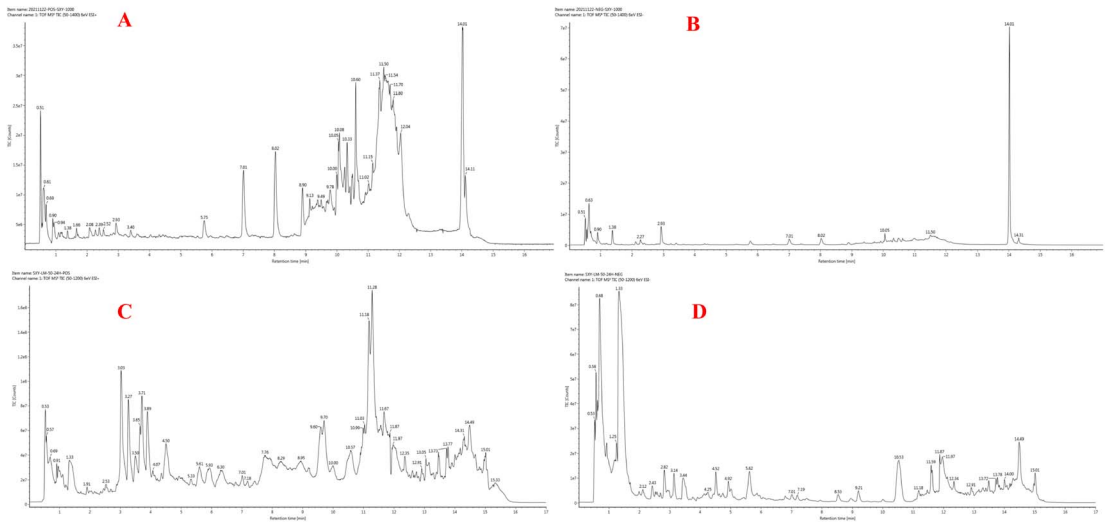

Fig. 9 Chromatographic analysis was performed on a Waters Acquity UPLC system, equipped with a binary pump solvent management system, an online degasser and an autosampler. All separations were carried out on an ACQUITY UPLC™ HSS T3 column (2.1 mm × 100 mm, 1.8 μm) at 45 °C. The mixture of (A) acetonitrile and (B) 0.1% (v/v) methanoic acid aqueous solution was chosen as the mobile phase using a gradient program: 0–2 min, 5–15% A; 2–8 min, 15–23% A; 8–11 min, 23–100% A; 11–13 min, 100–5% A; and stayed at 5% A for 4 min. The flow rate was 0.4 mL min^{-1} and the injection volume was 2 μL. UPLC-Q-TOF-MS chromatogram of MOL in positive ionization mode (A), and in negative ionization mode (B); UPLC-Q-TOF-MS chromatogram of MOS in positive ionization mode (C), and in negative ionization mode (D).

meanwhile, MSE supplementation can reduce body weight, obesity and inflammatory gene expression, improve glucose tolerance, and increase antioxidant gene expression.[46] Wang *et al.* extracted the polysaccharide component MOS-2-A from *M. oleifera* leaves.[103] Through experiments, they verified that MOS-2-A could reduce the number of pathogenic bacteria by increasing the number of beneficial bacteria, significantly improve the diversity of intestinal flora in mice, improve the structure of intestinal flora, and help maintain the integrity of intestinal mucosa, promote digestion and promote intestinal health. *M. oleifera* leaves induce the production of acetic acid, propionic acid and n-butyric acid after gastrointestinal digestion and colonic fermentation *in vitro*, resulting in a decrease in pH and promoting the growth of beneficial colonic bacteria.[40] In addition, more experimental results reveal that *M. oleifera* has the ability to regulate intestinal for the treatment of diseases.

Neuroprotective effect

Herbs therapy is widely used in the treatment of many diseases due to its low toxicity and good curative effect. *M. oleifera* has a variety of functions, including protective effects on the nervous system, due to its rich active ingredients.

M. oleifera is rich in flavonoids and polyphenols, which have neuroprotective effects. Di-(2-ethylhexyl) phthalate (DEHP) at specific concentrations can produce neurotoxic effects after prenatal and postnatal exposure. In rats, prenatal exposure to DEHP can disrupt the development of the central nervous system and reduce brain weight. It was found that *M. oleifera* extract can restore the activity of mitochondrial respiratory chain complex by regulating and reducing the formation of ROS, prevent oxidative injury by regulating Nrf2/HO-1 expression, and inhibit endoplasmic reticulum stress (ER stress) response to prevent neuron injury and protect neurons SH-SY5Y cells were protected from DEHP-induced apoptosis and maintained mitochondrial membrane permeability and caspase-3 activation, thus realizing the neuroprotective effect of *M. oleifera* extract on DEHP injury. *M. oleifera* seeds are rich in glucosinolates, such as niazimicin (NZ), the main bioactive substance.[104] Abdelsayed *et al.* found that NZ in *M. oleifera* seeds can play a neuroprotective role by affecting oxidative stress marker glutathione (GSH), malondialdehyde (MDA) inflammatory mediators NF-κB and NO neurotransmitters, dopamine and 5-hydroxytryptamine, and brain fatty acids (FA) levels in AlCl3-induced dementia rats.[105]

Ameliorate metabolic syndrome effect

Metabolic syndrome is a group of clinical syndromes with hypertension, central obesity, diabetes mellitus, hyperlipidemia and abnormal glucose metabolism. In modern times, people's life pressure, irregular work and rest, unreasonable diet structure and other factors lead to the low age of metabolic syndrome diseases, and become one of the main causes of death.[106] And studies have shown that *M. oleifera* can play a significant role in the treatment of these diseases.

Niazirin, a phenol glycoside isolated from *M. oleifera* seeds, could improve insulin resistance, hyperglycemia, hyperlipidemia, and non-alcoholic fatty liver disease. And in-depth investigation showed that niazirin can reduce the accumulation of gluconeogenesis and lipid, improve glycolysis and lipid oxidation by activating the AMP-Activated Protein Kinase (AMPK) pathway. These findings suggest that niazirin could serve as an effective treatment for metabolic syndrome.[1]

Additional studies have shown that *M. oleifera* leaf hydrolysate (MOLH), which is rich in phenols and peptides, can

Table 2 UPLC-Q-TOF-MS analysis of MOL and MOS

No.	t_R (min)	Ion type	*M*/*Z*		Error	The total number of pieces (ppm)	Formula	Compound name	Source
			Actual value	Theoretical value					
1	0.56	$[M-H]^-$	173.1042	174.1117	−1.4	156.0773 ($C_6H_{10}N_3O_2$), 131.0829 ($C_5H_{11}N_2O_2$)	$C_6H_{14}N_4O_2$	Arginine	MOL
2	0.56	$[M-H]^-$	154.0624	155.0695	1.2	137.0361 ($C_6H_5N_2O_2$), 93.0449 ($C_5H_5N_2$)	$C_6H_9N_3O_2$	Histidine	MOL
3	0.59	$[M+HCOO]^-$	264.109	219.1107	0.6	146.0461 ($C_5H_8NO_4$), 114.0196 ($C_4H_4NO_3$), 88.0413 ($C_3H_6NO_2$)	$C_9H_{17}NO_5$	Pantothenic acid	MOL
4	0.60	$[M-H]^-$	146.0461	147.0532	1.8	102.0564 ($C_4H_8NO_2$), 88.0413 ($C_3H_6NO_2$), 74.0254 ($C_2H_4NO_2$)	$C_5H_9NO_4$	Glitamic acid	MOL
5	0.60	$[M-H]^-$	118.0512	119.0582	2	104.0358 ($C_3H_6NO_3$), 102.0564 ($C_4H_8NO_2$), 74.0254 ($C_2H_4NO_2$)	$C_4H_9NO_3$	Threonine	MOL
6	0.60	$[M-H]^-$	132.0305	133.0375	1.7	114.0196 ($C_4H_4NO_3$), 88.0404 ($C_3H_6NO_2$), 74.0248 ($C_2H_4NO_2$)	$C_4H_7NO_4$	Aspartic acid	MOL
7	0.77	$[M-H]^-$	191.0561	192.0634	0.1	119.0352 ($C_4H_7O_4$), 101.0252 ($C_4H_5O_3$), 95.0143 ($C_5H_3O_2$)	$C_7H_{12}O_6$	Quinic acid	MOL
8	1.60	$[M+HCOO]^-$	326.1248	281.1263	0.9	173.0449 ($C_{10}H_7NO_2$), 164.0706 ($C_9H_{10}NO_2$), 147.0454 ($C_9H_7O_2$)	$C_{14}H_{19}NO_5$	Tyrosine	MOL
9	2.27	$[M-H]^-$	353.0875	354.0951	−0.8	179.0350 ($C_9H_7O_4$), 161.0244 ($C_9H_5O_3$), 133.0293 ($C_8H_5O_2$)	$C_{16}H_{18}O_9$	4-*O*-Caffeoylqunic acid	MOL
10	2.27	$[M-H]^-$	179.0345	180.0423	−2.7	161.0244 ($C_9H_5O_3$), 133.0293 ($C_8H_5O_2$), 109.0300 ($C_6H_5O_2$)	$C_9H_8O_4$	Caffeic acid	MOL
11	2.76	$[M-H]^-$	163.0406	164.0473	3	119.0502 (C_8H_7O), 93.0346 (C_6H_5O)	$C_9H_8O_3$	*trans*-4-Hydroxycinnamic acid	MOL
12	2.93	$[M+Na]^+$	543.1843	520.1945	1.2	423.1434 ($C_{24}H_{23}O_7$), 305.0985 ($C_{16}H_{17}O_6$)	$C_{26}H_{32}O_{11}$	(+)-Pi-noresinol-4-*O*-β-D-glucopyranoside	MOL
13	2.96	$[M+HCOO]^-$	375.0707	330.074	−3.8	195.0299 ($C_9H_7O_5$), 179.0354 ($C_9H_7O_4$), 161.0242 ($C_9H_5O_3$)	$C_{17}H_{14}O_7$	Cirsiliol	MOL
14	3.40	$[M+Na]^+$	421.3462	398.3549	4.9	343.3362 ($C_{25}H_{43}$)	$C_{28}H_{46}O$	24-Methylenecholesterol	MOL
15	3.40	$[M-H]^-$	593.1507	594.1585	−0.9	473.1089 ($C_{23}H_{21}O_{11}$), 323.551 ($C_{18}H_{11}O_6$), 161.0237 ($C_9H_5O_3$)	$C_{27}H_{30}O_{15}$	Vicenin 2	MOL
16	4.31	$[M+HCOO]^-$	324.1091	279.1107	0.6	132.0455 (C_8H_6NO), 89.0256 ($C_3H_5O_3$)	$C_{14}H_{17}NO_5$	Niazirin	MOL
17	5.34	$[M-H]^-$	609.1458	610.1534	−0.6	300.0275 ($C_{15}H_8O_7$), 301.0336 ($C_{15}H_9O_7$), 151.0043 ($C_7H_3O_4$)	$C_{27}H_{30}O_{16}$	Rutin	MOL
18	5.41	$[M-H]^-$	431.0985	432.1057	0.3	323.0528 ($C_{18}H_{11}O_6$), 117.0345 (C_8H_5O)	$C_{21}H_{20}O_{10}$	Cosmosiin	MOL
19	5.77	$[M-H]^-$	463.0881	464.0955	−0.2	300.0275 ($C_{15}H_8O_7$), 243.0299 ($C_{13}H_7O_5$), 151.0041 ($C_7H_3O_4$)	$C_{21}H_{20}O_{12}$	Isoquercitrin	MOL
20	6.95	$[M+HCOO]^-$, $[M-H]^-$	567.2081	522.2101	0	341.1402 ($C_{20}H_{21}O_5$), 311.0917 ($C_{18}H_{15}O_5$)	$C_{26}H_{34}O_{11}$	(+)-Isolariciresinol-3a-*O*-β-D-glucopyranoside	MOL
21	6.49	$[M-H]^-$	549.0877	550.0959	−1.6	505.0968 ($C_{23}H_{21}O_{13}$), 300.0273 ($C_{15}H_8O_7$), 151.0416 ($C_8H_7O_3$)	$C_{24}H_{22}O_{15}$	Quercetin-3-*O*-(6-malondiyl)-β-D-glucopyranoside	MOL
22	11.61	$[M+Na]^+$	491.3506	468.3604	2	412.3362 ($C_{28}H_{44}O_2$), 361.2872 ($C_{27}H_{37}$)	$C_{31}H_{48}O_3$	3β-Hydroxy-oleano-11,13 (18)-diene-28-carboxylic acid	MOL

Table 2 (*Contd.*)

No.	t_R (min)	Ion type	*M*/*Z*			The total number of pieces (ppm)	Formula	Compound name	Source
			Actual value	Theoretical value	Error				
23	7.02	$[M-H]^-$	447.0937	448.1006	0.9	284.0327 ($C_{15}H_8O_6$), 113.0617 ($C_6H_9O_2$)	$C_{21}H_{20}O_{11}$	Quercitrin	MOL
24	4.24	$[M-H]^-$	447.0926	448.0998	0.9	327.0522 ($C_{17}H_{11}O_7$), 297.0401 ($C_{16}H_9O_6$)	$C_{21}H_{20}O_{11}$	Astragalin	MOL
25	8.09	$[M+H]^+$	435.3604	412.3705	1.5	321.3120 ($C_{22}H_{41}O$), 209.2257 ($C_{15}H_{29}$)	$C_{29}H_{48}O$	Stigmastanol	MOL
26	8.09	$[M-H]^-$	591.1352	592.1428	−0.6	489.1038 ($C_{23}H_{21}O_{12}$), 284.0328 ($C_{15}H_8O_6$), 227.0350 ($C_{13}H_7O_4$)	$C_{27}H_{28}O_{15}$	Kaempferol-3-*O*-hydroxymethyl glutaryl hexanoside	MOL
27	8.10	$[M-H]^-$	533.0935	534.101	−0.4	489.1039 ($C_{23}H_{21}O_{12}$), 285.0412 ($C_{15}H_9O_6$)	$C_{24}H_{22}O_{14}$	Kaempferol-3-*O*-malondiacylhexanoside	MOL
28	8.90	$[M+Na]^+$	631.1258	608.1377	−1.9	325.0326 ($C_{17}H_9O_7$), 243.0162 ($C_9H_7O_8$), 201.0444 ($C_8H_9O_6$)	$C_{27}H_{28}O_{16}$	Quercetin - 3-*O*-hydroxymethyl glutaryl galactoside	MOL
29	9.78	$[M+Na]^+$	315.2331	314.2246	4	228.1527 ($C_{16}H_{20}O$), 176.1186 ($C_{12}H_{16}O$)	$C_{21}H_{30}O_2$	Progesterone	MOL
30	10.02	$[M+H]^+$	543.221	520.2309	1.7	431.1679 ($C_{23}H_{27}O_8$), 279.1438 ($C_{12}H_{23}O_7$)	$C_{27}H_{36}O_{10}$	Lariciresinol-9-*O*-β-D-glucopyranoside	MOL
31	10.09	$[M+Na]^+$, $[M+H]^+$	457.3696	456.3604	4.3	221.1942 ($C_{15}H_{25}O$), 101.1337 (C_7H_{17})	$C_{30}H_{48}O_3$	Oleanolic acid	MOL
32	10.51	$[M+HCOO]^-$	423.1663	378.1679	0.5	165.0194 ($C_8H_5O_4$), 109.0293 ($C_6H_5O_2$)	$C_{20}H_{26}O_7$	1-(4-Hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxypropyl)-2	MOL
33	11.70	$[M+Na]^+$	453.3682	430.3811	−4.6	245.1536 ($C_{16}H_{21}O_2$), 227.2369 ($C_{15}H_{31}O$), 209.2264 ($C_{15}H_{29}$)	$C_{29}H_{50}O_2$	Vitamin E	MOL
34	0.60	$[M-H]^-$	132.0298	133.037	−3.63	115.0031 ($C_4H_3O_4$), 88.0406 (C3H6NO2), 74.0252 ($C_2H_4NO_2$)	$C_4H_7NO_4$	Aspartic acid	MOS
35	0.61	$[M-H]^-$	146.0453	147.0526	−3.66	102.0558 ($C_4H_8NO_2$), 88.0406 ($C_3H_6NO_2$), 74.0252 ($C_2H_4NO_2$)	$C_5H_9NO_4$	Glitamic acid	MOS
36	0.90	$[M+HCOO]^-$	150.0408	105.0426	0.23	87.0090 ($C_3H_3O_3$), 59.0147 ($C_2H_3O_2$)	$C_3H_7NO_3$	Serine	MOS
37	1.09	$[M+H]^+$	147.1134	146.1062	4.29	135.1137 ($C_{10}H_{15}$), 128.0944 ($C_6H_{12}N_2O$)	$C_6H_{14}N_2O_2$	Lysine	MOS
38	1.25	$[M+HCOO]^-$	326.1223	281.1263	−6.92	164.0714 ($C_9H_{10}NO_2$), 105.0345 (C_7H_5O)	$C_{14}H_{19}NO_5$	Tyrosine	MOS
39	1.80	$[M+HCOO]^-$	399.0948	354.0966	3.83	209.0442 ($C_{10}H_9O_5$), 149.0237 ($C_8H_5O_3$), 108.0213 ($C_6H_4O_2$)	$C_{16}H_{18}O_9$	4-*O*-Caffeoyl-quinic acid	MOS
40	2.06	$[M-H]^-$	218.1029	219.1102	−2.22	146.0816 ($C_6H_{12}NO_3$), 99.0450 ($C_5H_7O_2$)	$C_9H_{17}NO_5$	Pantothenic acid	MOS
41	2.46	$[M+H]^+$	521.2372	520.23	−1.69	405.1908 ($C_{22}H_{29}O_7$), 375.1834 ($C_{21}H_{27}O_6$)	$C_{27}H_{36}O_{10}$	Lariciresinol-9-*O*-β-D-glucopyranoside	MOS
42	2.82	$[M-H]^-$	353.0867	354.094	−3.2	184.0715 ($C_9H_{12}O_4$), 143.0357 ($C_8H_6O_2$), 23.0812 ($C_{12}H_{14}O_5$)	$C_{16}H_{18}O_9$	Chlorogenic acid	MOS
43	2.83	$[M+HCOO]^-$	579.0977	534.0995	−2.55	169.0495 ($C_8H_9O_4$), 143.0340 ($C_6H_7O_4$), 95.0133 ($C_5H_3O_2$)	$C_{24}H_{22}O_{14}$	Kaempferol-3-*O*-malondiacylhexanoside	MOS
44	3.10	$[M+HCOO]^-$	243.0502	198.052	−3.48		$C_9H_{10}O_5$	Syringic acid	MOS

Table 2 (*Contd.*)

No.	t_R (min)	Ion type	*M*/*Z* Actual value	*M*/*Z* Theoretical value	Error	The total number of pieces (ppm)	Formula	Compound name	Source
						164.0460 ($C_9H_8O_3$), 134.0370 ($C_8H_6O_2$)			
45	3.22	$[M + HCOO]^-$	389.0886	344.0904	2.15	193.0501 ($C_{10}H_9O_4$), 178.02724 ($C_9H_6O_4$)	$C_{18}H_{16}O_7$	Cirsilineol	MOS
46	4.44	$[M + H]^+$	595.1425	594.1352	−3.58	167.0353 ($C_8H_7O_4$), 161.0242 ($C_9H_5O_3$)	$C_{30}H_{26}O_{13}$	Procyanidin	MOS
47	4.46	$[M - H]^-$	179.0345	180.0418	−2.68	161.0238 ($C_9H_5O_3$), 133.0295 ($C_8H_5O_2$), 109.0295 ($C_6H_5O_2$)	$C_9H_8O_4$	Caffeic acid	MOS
48	7.56	$[M + HCOO]^-$	509.0961	464.0979	4.76	299.0196 ($C_{15}H_8O_7$), 243.0289 ($C_{13}H_7O_5$), 151.0025 ($C_7H_3O_4$)	$C_{21}H_{20}O_{12}$	Isoquercitrin	MOS
49	4.68	$[M + HCOO]^-$	223.0242	178.026	−2.86	125.0237 ($C_6H_5O_3$), 109.0290 ($C_6H_5O_2$)	$C_9H_6O_4$	Esculetin	MOS
50	7.13	$[M - H]^-$, $[+HCOO]^-$	609.1529	610.1534	−0.86	300.0254 ($C_{15}H_8O_7$), 301.0339 ($C_{15}H_9O_7$), 167.0322 ($C_8H_3O_4$)	$C_{27}H_{30}O_{16}$	Rutin	MOS
51	4.93	$[M - H]^-$, $[+HCOO]^-$	289.0715	290.0788	−0.78	167.0711 ($C_9H_{11}O_3$), 137.0239 ($C_7H_5O_3$), 108.0214 ($C_6H_4O_2$), 179.0341 ($C_9H_7O_4$)	$C_{15}H_{14}O_6$	(−)-Epicatechin	MOS
52	5.57	$[M - H]^-$	593.1505	594.1578	−1.09	473.1081 ($C_{23}H_{21}O_{11}$), 323.0546 ($C_{18}H_{11}O_6$), 161.0235 ($C_9H_5O_3$)	$C_{27}H_{30}O_{15}$	Vicenin 2	MOS
53	5.63	$[M + HCOO]^-$, $[-H]^-$	324.1087	279.1105	−0.4	132.0450 (C_8H_6NO), 89.0247 ($C_3H_5O_3$)	$C_{14}H_{17}NO_5$	Niazirin	MOS
54	5.64	$[M + Na]^+$	464.1288	441.1395	−0.29	185.0457 ($C_{11}H_7NO_2$), 171.0299 ($C_{10}H_5NO_2$)	$C_{19}H_{19}N_7O_6$	Folic acid	MOS
55	5.70	$[M + HCOO]^-$	361.0554	316.0572	−2.94	165.0541 ($C_9H_9O_3$), 122.0367 ($C_7H_6O_2$), 145.0285 ($C_9H_5O_2$)	$C_{16}H_{12}O_7$	Isorhamnetin	MOS
56	5.92	$[M - H]^-$	447.0914	448.0987	−4.11	3270495 ($C_{17}H_{11}O_7$), 297.0397 ($C_{16}H_9O_6$)	$C_{21}H_{20}O_{11}$	Astragalin	MOS
57	5.98	$[M - H]^-$	163.0393	164.0466	−4.79	119.0500 (C_8H_7O), 117.0337 (C_8H_5O), 93.0351 (C_6H_5O)	$C_9H_8O_3$	*trans*-Cinnamic acid	MOS
58	6.66	$[M + HCOO]^-$	539.1219	494.1237	4.48	179.0340 ($C_9H_7O_4$), 151.0389 ($C_8H_7O_3$), 135.0448 ($C_8H_7O_2$)	$C_{26}H_{22}O_{10}$	Salvianolic acid A	MOS
59	6.72	$[M - H]^-$	475.0904	476.0976	4.56	304.0604 ($C_{15}H_{12}O_7$), 286.0494 ($C_{15}H_{10}O_6$), 125.0244 ($C_6H_5O_3$)	$C_{22}H_{20}O_{12}$	Kaempferol-3-*O*-(6″-acetyl glucoside)	MOS
60	6.80	$[M - H]^-$	193.0497	194.057	−4.82	180.0417 ($C_9H_8O_4$), 133.0285 ($C_8H_5O_2$), 108.0221 ($C_6H_4O_2$)	$C_{10}H_{10}O_4$	Ferulic acid	MOS
61	7.01	$[M + H]^+$	743.2399	742.2327	0.87	473.1683 ($C_{21}H_{29}O_{12}$), 397.1092 ($C_{18}H_{21}O_{10}$), 313.0964 ($C_{14}H_{17}O_8$)	$C_{33}H_{42}O_{19}$	Troxerutin	MOS
62	7.07	$[M - H]^-$	317.1028	318.11	−0.97	255.0651 ($C_{15}H_{11}O_4$), 135.0081 ($C_7H_3O_3$), 108.0214 ($C_6H_4O_2$)	$C_{17}H_{18}O_6$	Evofolin B	MOS
63	6.52	$[M + HCOO]^-$	567.2052	522.2101	−2.05	451.1628 ($C_{22}H_{27}O_{10}$), 311.0917 ($C_{18}H_{15}O_5$)	$C_{26}H_{34}O_{11}$	(+)-Isolariciresinol-3a-*O*-β-D-glucopyranoside	MOS
64	7.20	$[M - H]^-$	431.0983	432.1055	−0.27	323.0555 ($C_{18}H_{11}O_6$), 117.0343 (C_8H_5O)	$C_{21}H_{20}O_{10}$	Cosmosiin	MOS

Table 2 (*Contd.*)

No.	t_R (min)	Ion type	*M*/*Z*			The total number of pieces (ppm)	Formula	Compound name	Source
			Actual value	Theoretical value	Error				
65	7.20	$[M-H]^-$	431.0983	432.1055	−0.27	253.0492 ($C_{15}H_9O_4$), 145.0273 ($C_9H_5O_2$), 93.0347 (C_6H_5O)	$C_{21}H_{20}O_{10}$	Isovitexin	MOS
66	7.20	$[M-H]^-$	283.0606	284.0679	−2.17	151.0029 ($C_7H_3O_4$), 145.0273 ($C_9H_5O_2$), 117.0343 (C_8H_5O)	$C_{16}H_{12}O_5$	Acacetin	MOS
67	7.38	$[M-H]^-$	285.0395	286.0468	−3.42	152.0113 ($C_7H_{14}O_4$), 125.0239 ($C_6H_5O_3$), 108.0214 ($C_6H_4O_2$)	$C_{15}H_{10}O_6$	Luteolin	MOS
68	8.37	$[M-H]^-$	549.0867	550.0939	−3.53	505.0974 ($C_{23}H_{21}O_{13}$), 300.0269 ($C_{15}H_8O_7$), 151.0391 ($C_8H_7O_3$)	$C_{24}H_{22}O_{15}$	Quercetin-3-*O*-(6-malondiyl)-β-D-glucopyranoside	MOS
69	8.89	$[M-H]^-$	447.0919	448.0992	−3.14	284.0316 ($C_{15}H_8O_6$), 93.0349 (C_6H_5O)	$C_{21}H_{20}O_{11}$	Quercitrin	MOS
70	9.57	$[M+HCOO]^-$	317.0657	272.0675	−3.16	162.0296 ($C_9H_6O_3$), 147.0431 ($C_9H_7O_2$)	$C_{15}H_{12}O_5$	Naringenin	MOS
71	9.93	$[M+HCOO]^-$	359.0756	314.0774	−4.64	283.0592 ($C_{16}H_{11}O_5$), 178.0256 ($C_9H_6O_4$)	$C_{17}H_{14}O_6$	Cirsimaritin	MOS
72	10.03	$[M-H]^-$	591.1343	592.1416	−2.07	489.1033 ($C_{23}H_{21}O_{12}$), 284.0312 ($C_{15}H_8O_6$), 227.0343 ($C_{13}H_7O_4$)	$C_{27}H_{28}O_{15}$	Kaempferol-3-*O*-hydroxymethyl glutaryl hexanoside	MOS
73	10.36	$[M+HCOO]^-$	433.1487	388.1505	−4.04	373.1269 ($C_{20}H_{21}O_7$), 341.1032 ($C_{19}H_{17}O_6$), 181.0484 ($C_9H_9O_4$)	$C_{21}H_{24}O_7$	Medioresinol	MOS
74	11.01	$[M-H]^-$, $[+HCOO]^-$	359.1482	360.1555	−4.91	329.1376 ($C_{19}H_{21}O_5$), 314.1159 ($C_{18}H_{18}O_5$), 180.0777 ($C_{10}H_{12}O_3$)	$C_{20}H_{24}O_6$	(7*S*,8*R*)-Dihydrodehydrodiguaiacyl alcohol	MOS
75	12.57	$[M+H]^+$	719.1617	718.1544	1.38	535.1587 ($C_{29}H_{27}O_{10}$), 193.0839 ($C_{22}H_{13}O_3$), 149.0585 ($C_9H_9O_2$)	$C_{36}H_{30}O_{16}$	Salvianolic acid B	MOS
76	13.14	$[M+Na]^+$	553.1343	530.1451	4.86	396.10618 ($C_{18}H_{20}O_{10}$), 237.1079 ($C_{13}H_{17}O_4$)	$C_{26}H_{26}O_{12}$	3,4-Di-*O*-caffeoylquinic	MOS
77	13.40	$[M+Na]^+$	543.184	520.1949	0.88	421.1275 ($C_{24}H_{21}O_7$), 340.1154 ($C_{16}H_{20}O_8$)	$C_{26}H_{32}O_{11}$	(+)-Pi-noresinol-4-*O*-β-D-glucopyranoside	MOS
78	13.74	$[M+H]^+$	469.3669	468.3596	−1.62	413.3384 ($C_{28}H_{45}O_2$), 361.28765 ($C_{27}H_{37}$)	$C_{31}H_{48}O_3$	3β-Hydroxy-oleano-11,13 (18)-diene-28-carboxylic acid	MOS

Table 3 Health benefits of *M. oleifera*

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
Antioxidant and anti-inflammatory effect	Paw edema and peritonitis	Female Swiss (*Mus musculus*) mice	*In vivo*	15 mg kg^{-1}, 30 mg kg^{-1}	*M. oleifera* flowers trypsin inhibitor (MoFTI)	Reduced leukocyte migration, plasma extravasation (attributed to lower protein content), and the levels of NO and pro-inflammatory (tumor necrosis factor-α, interleukin IL-6, and IL-17A) and anti-inflammatory (IL-4 and IL-10) cytokines	Promote anti-inflammatory activity	60
	—	Chang liver cells	*In vitro*	2 mg mL^{-1}, 4 mg mL^{-1}, 6 mg mL^{-1}, 250 mg mL^{-1}	*M. oleifera* seeds protein hydrolysate (FM3)	Increasing the activities of endogenous antioxidant enzymes SOD and CAT, and scavenging intracellular ROS	Protect hepatocytes from oxidative stress damage. May be used as potential antioxidants or protective agents against oxidative damage to cells	61
	Diabetic nephropathy	HRMC cell, Sprague Dawley rats	*In vitro*, *in vivo*	200 mg kg^{-1}	*M. oleifera* seeds extract (MOS)	Antioxidant and anti-renal fibrosis activities by increasing the activity of GSK-3β and the expression of Nrf2 and HO-1	Delay the progression of diabetic nephropathy by improving renal function and reducing patho-physiological changes	62
	Male reproductive system health	Wistar male rats	*in vivo*	0.55 mg kg^{-1}, 1.10 mg kg^{-1} and 2.20 mg kg^{-1}	*M. oleifera* leaves tea (total phenols, flavonoids, and antioxidants)	Increase sertoli cells and the total spermatogenic cells; scavenged DPPH radical, ABTS radical and H_2O_2, and inhibit the formation of LPO and AGEs	Rich total phenols, flavonoids, and antioxidants could enhance sexual function and the male reproductive system. Increased the courtship behavior, seminiferous tubule diameter, epithelium height, epithelium area, type A spermatogonia, and spermatogonia efficiency	32
	Rat paw edema	RAW 264.7 murine cell, Sprague Dawley rats	*In vitro*, *in vivo*	1 μM, 5 μM, 33 mg kg^{-1}	*M. oleifera* seed extract (MSE)	MIC-1 decreased inflammatory signaling (NO production, gene expression of iNOS, IL-1β, IL-6) and promoted detoxification (gene expression of NQO1, HO1, GSTP1) in LPS-stimulated murine macrophages	Anti-inflammatory and antioxidant properties *in vivo* and *in vitro*	63

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
	—	Murine macrophage cell line RAW 246.7	*In vitro*	50 μg mL^{-1}, 100 μg mL	*M. oleifera* leaves protein hydrolysate (MOPH)	Peptides remove DDPH and ABTS radicals and exhibit strong ORAC determination activity. Increase in the number of exposed amino acid residues and promote an increase in scavenging activity; inhibits NO production and acts as an anti-inflammatory	Antioxidant and anti-inflammatory activity	56
Antioxidant and anti-inflammatory effect	Hepatic inflammation	Healthy adult male mice	*In vivo*	100 mg kg^{-1}, 200 mg kg^{-1}, 400 mg kg^{-1}	*M. oleifera* leaves extract (MOLE)	Modulated TLR4/NF-κB pathway, suppressed TLR4 and NF-κB gene expression and as well as TLR4 and NF-κB-p65 protein expression. Protects from apoptotic cell death *via* antioxidative and anti-inflammatory impacts with consequent attenuation of DNA-induced genotoxicity	Protective role against hepatotoxicity	64
	Ageing	Wistar albino rats	*In vivo*	200 mg per kg per body weight	*M. oleifera* leaves (MOAE)	Reduced lipid peroxidation and lipofuscin pigmentation increased serotonin and antioxidant enzymes	Protective effect on age-related cerebral oxidative stress	65
	Stomach and forestomach ulceration	*E. coli*, *P. aeruginosa*, *S. aureus*, Sprague-Dawley male rats	*In vivo*, *in vitro*	100–500 μg mL^{-1}, 100 mg kg^{-1}	*M. oleifera* leaves extract	Hydrochloric acid secretion neutralization effect in gastric mucosa, decreased MDA level and increasing antioxidant enzyme activity (CAT, SOD, GPx)	Anti-ulcer effect, protect the gastric ulcer	66
		Wistar albino male rats	*In vivo*	200 mg per kg body wt	*M. oleifera* aqueous extract	Reduces oxidative stress-induced DNA damage by improving NF-kB and TNF-α, restoring lead disturbance, preserving hepatocyte integrity and reducing serum liver enzyme activity	Alleviated lead-induced adverse effects	67
Antitumor effect	Human breast cancer cells	Breast cancer cells, T-47D and MDA-MB-231	*in vitro*	0.25 μg mL^{-1}, 5 μg mL^{-1}, 10 μg mL^{-1}, 15 μg mL^{-1}, 20 μg mL^{-1}, 40 μg mL^{-1}, 80 μg mL^{-1}, 100 μg mL^{-1}	*M. oleifera* leaves methanolic extract (MOME)	Antiproliferative effect on T-47D and MDA-MB-231. The phosphatidylserine exposure on the membrane of the cells confirmed the mitochondria mediated intrinsic apoptosis induction in the MOME treated cells	Contributes to cell cycle arrest and inhibits the proliferation of breast cancer cells	68

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
Antitumor effect	MDA-MB-231 cells	MDA-MB-231 cells, Female mice	*In vitro*, *in vivo*	A high-fat diet (HFD) supplemented with 0.6% w/w MC	*M. oleifera* seeds concentrate (MC)	Decreased fasting blood glucose and increased insulin sensitivity in mice after obesity attack. Decreased protein expression of CD31	Protected against high-fat diet- and chemotherapy-induced increases in fasting glucose and improved insulin sensitivity	69
	A549 lung and SNO oesophageal cancer	A549 lung and SNO oesophageal cancer cells	*In vitro*	1.575–393.83 μg mL^{-1}	AuNP synthesized from MO aqueous leaf extracts (MLAuNP)	Increased caspase activity in SNO cells and PS externalization, $\Delta\Psi_m$, caspase-9, caspase-3/7 activities, and decreased ATP levels in A549 cells. Increased, p53 mRNA and protein levels, SRp30a ($P = 0.428$), Bax, Smac/DIABLO and PARP-1 24 kDa fragment levels and protein levels and activated alternate splicing with caspase-9a splice variant. Decreased Bcl-2, Hsp70, Skp2, Fbw7α, c-myc Mrna	No cytotoxic to PBMCs, pro-apoptotic properties were confirmed in A549 and SNO cells	70
	The human pancreatic epithelioid carcinoma	PANC-1 cell, immune deficient athymic CD-1 nude mice	*In vivo*	0.5, 1.0, and 1.5 mg g^{-1}, 200 μL per mouse	*M. oleifera* aqueous leaves extract	Induction of apoptosis. Decreased expression of the pro-apoptotic protein Bcl-2, and downregulated the key component of DNA repair pathways PARP-1 and the NF-κB-related proteins IκB-α, p65-subunit, and COX-2	Antiproliferative and antiangiogenic effects, decreased pancreatic cancer cell survival and metastatic activity and inhibited tumor growth	71
	Colorectal cancer	CD-1 male (ICR) mice	*In vivo*	2.5% w/w and 5% w/w	*M. oleifera* leaves powder	Reduce the activity of harmful faecal enzymes (β-glucosidase, β-glucuronidase, tryptophanase and urease)	Diminish colonic lesions and decrease the activity of fecal harmful enzymes such as β-glucosidase, β-glucuronidase, tryptophanase and urease	72
	Hepatocellular carcinoma	Wistar male rats	*In vivo*	500 mg kg^{-1}	*M. oleifera* leaf ethanol extract (MOLEE)	Reduce Bcl-2 and Bcl-xL and the up-regulation of Bax and caspase 3, and reduced the expression level of β-arrestin-2 mRNA, thus promoting apoptosis signal transduction	Against DEN-induced HCC by exerting antioxidant and apoptotic activities	73

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
	Sarcoma	Sarcoma 180 cells, Swiss female mice	*In vitro*, *in vivo*	24.6–25 μg mL^{-1}, 15 or 30 mg kg^{-1}	*M. oleifera* flower trypsin inhibitor (MoFTI)	Upregulation of pro-apoptotic proteins and the downregulation of anti-apoptotic proteins (*e.g.*, Bcl-2 and Bcl-xl), caspase activation, and cytochrome c release. Induce ROS production and DNA fragmentation, suppress extracellular-signal-regulated kinase (ERK) activity, disrupt the cell cycle, and cause mitochondrial membrane damage	Cytotoxic to sarcoma 180 cells, reduce in tumor weight and antiangiogenic effect	74
Gut protective and regulation of intestinal flora effect	Hymenolepiasis nana	Female Swiss albino mice	*In vivo*	400 mg per kg body weight	*M. oleifera* leaves extract	Decreased TGF-β, IFN-y and MMC counts *versus* increased GC counts, T-helper cell type 2 (Th2) cytokines and IgA level achieve protection against *H. nana* infections	Anti-inflammatory and induce protection against *H. nana* infection	75
	Adiposity	C57BL/6J male mice	*In vivo*	Dietary supplementation with 0.34%MIC-1 (0.73%MSE)	*M. oleifera* seed extract (MSE)	Activate Nrf2 and its downstream targets and/or regulation of gut microbiota, MSE activates Nrf2 and its downstream targets and/or modulates the gut microbiota. MIC-1 has antibiotic properties, making it an, affecting host metabolism by regulating energy balance, glucose metabolism, lipid metabolism, and inflammation	Reduce body weight, obesity and inflammatory gene expression, improve glucose tolerance, and increase antioxidant gene expression	46
	—	C57BL/6 mice	*In vivo*	40 mg kg^{-1}, 60 mg kg^{-1}	*M. oleifera* polysaccharides	Inhibit the expression levels of IL-6 and TNF-α, affecting immune repertoire and change immune state	Regulate the intestinal flora, increase the relative abundance of beneficial bacteria and reduce the relative abundance of harmful bacteria, promoting intestinal health	54

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
	—	C57BL/7 mice	*In vivo*	20 mg kg^{-1}, 40 mg kg^{-1}, 61 mg kg^{-1}	*M. oleifera* polysaccharides	Reduced glucose, total cholesterol, and malondialdehyde. Improved superoxide dismutase and catalase in serum. Modulates the microbiological balance of the gut by increasing the abundance of good bacteria and decreasing the abundance of bad bacteria in the gut	Improve serum index, intestinal morphology, caecal microflora in mice and the villi length and crypt depth in both ileum and jejunum; increased the ratio of villi length to crypt depth in jejunum. Affecting the function of microbiota	52
	—	Stool samples from healthy participants	*In vitro*	The stool suspension was loaded into sterile anaerobic jars containing 50 mg polysaccharide samples	*M. oleifera* root polysaccharides (MRP)	Improve the intestinal environment by producing short-chain fatty acids by intestinal flora fermentation, and maintain intestinal homeostasis by controlling the composition of intestinal flora	Increased the content of beneficial microflora and decreased the abundance of harmful microflora	76
Neuroprotective effect	Glutamate-induced DNA damage in RGCs	RGCs cells	*In vitro*	10 μg mL^{-1}, 50 μg mL^{-1},[45] μg mL	*M. oleifera* seeds extract	Increase neuronal cell viability and minimal cellular injury, extend branches in neurons, modulate axonal development, and promote synaptogenesis	Neuroprotective effects	77
Neuroprotective effect	Neurodegenerative	Periodontal tissue cell	*In vitro*	0.5 μM	Moringin was isolated from *M. oleifera* seeds	Increased the expression of genes involved in neuron cortical development and in particular in neuron belonging to upper and deep cortical layers, involved in osteogenesis and adipogenesis	Promote and accelerate cortical neuronal differentiation of hPDLSCs to improve stem cell therapy for neurological diseases	78
	—	PC12 cells	*In vitro*	0.01 μM, 0.1 μM, 1 μM, 10 μM, 50 μM, and 100 μM	Pyrrole-2-carbaldehydes from *M. oleifera* seeds (pyrrolemorines A–G)	Against oxygen-glucose deprivation/reperfusion injury in PC12 cells by regulating NF-κb and Nrf2	Pyrrolemorines A, E, and pyrrolemarumine displayed neuroprotective activities, and ttenuate PC12 cell damage induced by oxygen glucose deprivation	79
	Peripheral nerve injury (PNI)	Adult male albino mice (BALB/c)	*In vivo*	200 mg per kg body weight	*M. oleifera* leaves extract	Promoting effects of *M. oleifera* might be attributed to the flavonoid class	Prove a valuable target for the discovery of effective and affordable intervention against peripheral nerve injuries	80

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
Ameliorate metabolic syndrome effect	NAFLD	ICR mice, L02 cells	*In vivo*, *in vitro*	50 mg kg^{-1}, 100 mg kg^{-1}, and 200 mg kg^{-1}, 0.2, 0.4, 0.6, 0.8, and 1 mM	*M. oleifera* seed extract containing 1-*O*-(4-hydroxy-methylphenyl)-α-L-rhamno-pyranoside (GR)	Inhibits lipid accumulation in L1 cells by regulating AMPK/mTOR/SREBP-02 and PPARα pathways. GR anti-inflammatory can promote PPARα and AMPK, inhibiting downstream mTOR/SREBP-1, activating lipoprotein lipase and changing gene coding enzyme to induce transcription and participate in lipid and lipoprotein metabolism, improve the release of intracellular reactive oxygen species, reduce the accumulation of oil and TG, and promote lipid metabolism	Decreased serum fat content, inhibited liver injury, and increased antioxidant mechanism	81
	Diabetes	Wister male rats	*In vivo*	500 mg kg^{-1}, 250 mg kg^{-1} and 500 mg kg^{-1}	*M. oleifera* leaves methanolic leave extracts (MO)	Reduced inflammation and oxidative stress, reducing hyperglycemia-related liver damage	Reduced fasting plasma ALAT, ASAT, GGT, increased plasma albumin, and restored the damage hepatocellular architecture	82
	Diabetes	Pre-diabetic subjects aged 40 to 70 years who have not used medication to control glycemic	*In vivo*	1600 mg per day	*M. oleifera* leaves capsule	TNF-α to be a key factor to identify potential respondents	The beneficial effect on blood glucose control in pre-diabetic patients	83
Ameliorate metabolic syndrome effect	Diabetes and NAFLD	C57BL/6 mice	*In vivo*	250 mg kg^{-1}	*M. oleifera* fermentation extract (FM)	Reduced high fat diet-induced ER stress, oxidative stress, lipid toxicity of quadriceps muscle and proinflammatory cytokine mRNA expression in the liver, epididymal adipose tissue, and quadriceps of HFD-fed mice, glucose intolerance and NAFLD in HFD-induced obesity by reducing ER stress, oxidative stress, and inflammation	Antidiabetic effects and can be an effective dietary supplement for treating hyperglycemia and NAFLD	84

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
	T2DM	UCD T2DM rats	*In vivo*	202 mg per kg per day, 94 mg per kg per day	*M. oleifera* seeds extract	Reduced inflammatory markers (KC/GRO and TNF-α). MS has anti-inflammatory activity by activating Nrf2 pathway	Delayed onset of diabetes in rat models of ucd T2DM	85
	Hypertensive	Wistar Kyoto male rats	*In vivo*	750 mg per day per rat	*M. oleifera* (MOI) seed powder	Decreased the level of free 8-isoprostaglandin circulation and the expressions of iNOS and NF-κB protein were decreased, up-regulated the expressions of p^{22phox} and p^{47phox} and SOD2	Vascular antioxidant, anti-inflammatory, and endothelial protective effects in SHR. Combat cardiovascular diseases associated with oxidative stress and inflammation	86
Other	Reproductive protection	NIH Swiss female and male mice	*In vivo*	Diet supplemented with 4% MOL, diet supplemented with 8% MOL	*M. oleifera* leave (MOL) powder	Decreased serum MDA in both male and female mice, reduced the rate of sperm abnormality in male, and the expression of Bax	Affecting reproductive	87
	—	NZW rabbits	*In vivo*	5 g kg^{-1}, 10 g kg^{-1} and 15 g kg^{-1}	*M. oleifera* leaves extract	Attenuate phytoestrogenic pituitary–gonadal axis, and reduced serum gonadotropin (FSH and LH) and oestrogen concentration in does	Female rabbits: reductions in serum FSH, LH, and estrogen concentrations. Male rabbits: increased, FSH and LH, and decreased the serum testosterone concentration. Improved semen volume, sperm count and motility were significantly	88
	—	Sprague Dawley male rats	*In vivo*	800 mg kg^{-1}	*M. oleifera* aqueous extract	*R*educes the oxidative stress in a unilateral cryptorchidism induced rats, and attenuate histopathological damages, HSP expression and germ cell apoptosis	Increased apoptotic cells in the undescended testes. Decreased pathological damages, oxidative stress, expression level of HSP70 and apoptosis	20

Table 3 (*Contd.*)

Effect	Disease	Subjects	Model	Dose	Components	Mechanism of action	Functional properties	Ref.
Other	Promote wound healing	*P. aeruginosa*, *S. aureus*, and *E. coli*, Swiss albino male mice	*In vivo*, *in vitro*	100 mg mL^{-1}, 10% hydrogel was formulated using 10 g of *M. oleifera n*-hexane seed extract and 90 g of gel	*M. oleifera* seeds extract	Antioxidant, antimicrobial, and wound healing activitie. Gram-positive and Gram-negative bactericidal potential	Could be used as potential herbal wound healing agents	89
	Diabetic foot ulcers	Wister male rats	*In vivo*	0.5%, 1%, and 2% w/w aqueous fraction	*M. oleifera* leaves extract	Decreased wound size, improved wound contraction, and tissue regeneration, as well as downregulation of inflammatory mediators, such as TNF-α, IL-1β, IL-6, inducible nitric oxide synthase, and cyclooxygenase-2, and upregulate an angiogenic marker vascular endothelial growth factor in wound tissue	Vicenin-2 active compound may accelerate wound healing in hyperglycemic condition	90
	Bone protection	Early osteoblasts resulting from neonatal rats	*In vitro*, *in vivo*	25 $\mu g\ mL^{-1}$, 50 $\mu g\ mL^{-1}$, 100 $\mu g\ mL^{-1}$ and 150 $\mu g\ mL^{-1}$, 1 $g\ kg^{-1}$	*M. oleifera* polysaccharides	Reduced apoptosis and intracellular ROS levels in glucocorticoid-induced femoral necrosis. Decreased the expression of TNF-α and IL-6 genes with polysaccharide, and increased the expression of OCN, RUNX2 and COL-1 genes in cartilage tissue, protecting femoral head necrosis	Controlling and regenerating osteoblasts cells, and preventing necrosis of the femoral head	91

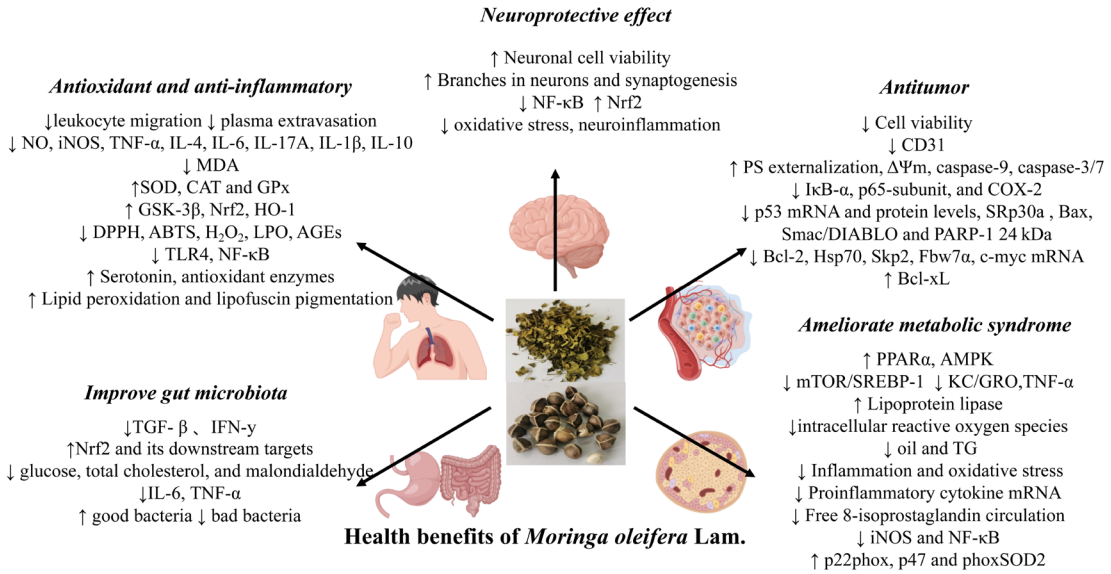

Fig. 10 Summary of the potential health benefits of *M. oleifera*. (Images were obtained from http://figdraw.com/).

improve hyperuricemia and metabolic disorders.[107] To verify the therapeutic effect of 1-*O*-(4-hydroxy-methylphenyl)-α-L-rhamnopyranoside (GR) in *M. oleifera* seeds on non-alcoholic fatty liver disease (NAFLD), *in vitro* and *in vivo* experiments were established. The results showed that GR could significantly reduce intracellular fat deposition and ROS content, up-

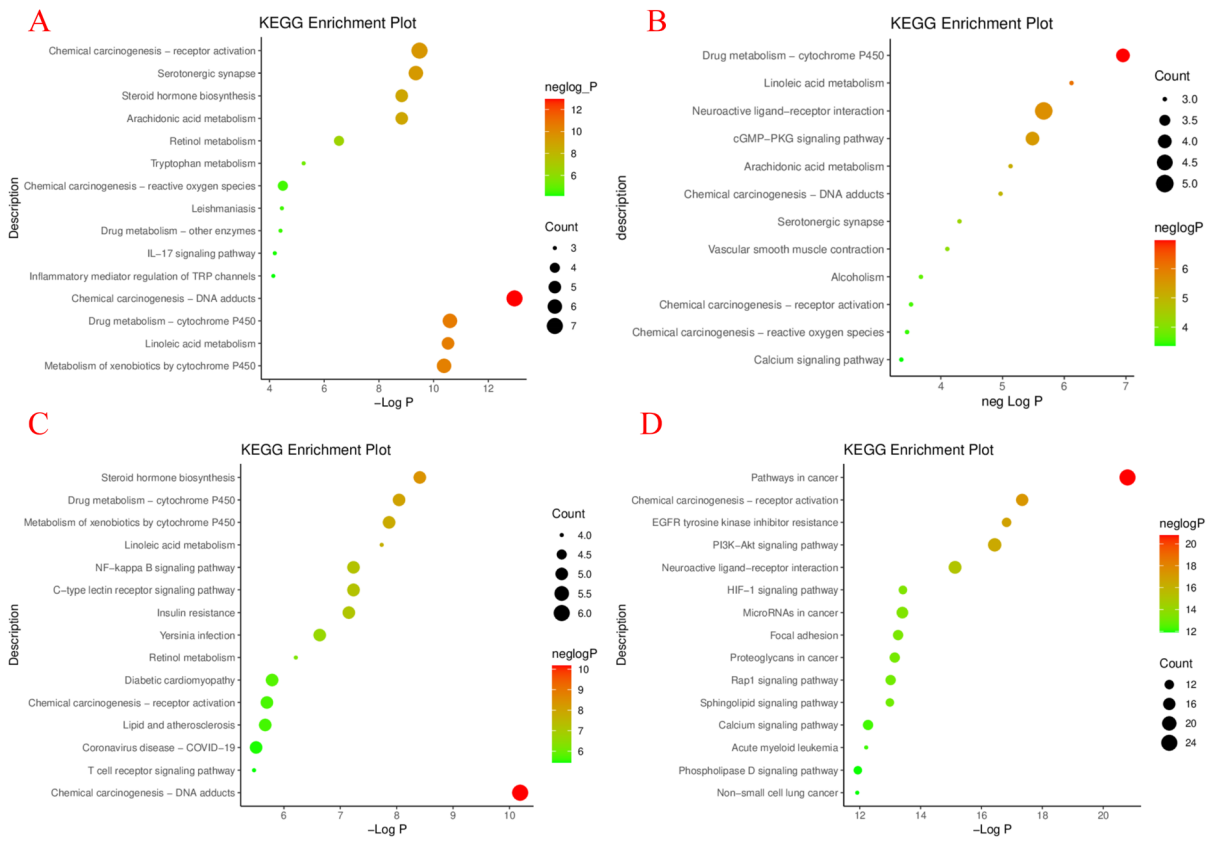

Fig. 11 The common target of *M. oleifera* and 4 diseases obtained by the above screening was imported into the Metascape Data platform (https://metascape.org/gp/index.html#/main/step1).[117] The species was set to be "*Homo sapiens*", and GO function enrichment analysis and KEGG pathway enrichment was performed. GO functional analysis includes biological process (BP, biological process), cellular component (CC, cellular component), molecular function (MF, molecular function). It is visualized as histogram and bubble chart by the ImageGP (https://www.bic.ac.cn/ImageGP/).[115] KEGG enrichment analysis of potential targets of MOL in treating 4 diseases: arthritis (A), hypertension (B), diabetes (C), tumor (D).

regulate AMPK and peroxisome proliferator-activated receptor (PPARα), down-regulate Mechanistic Target of Rapamycin (mTOR) and sterol regulatory element binding transcription factor 1 (SREBP-1) to achieve liver lipid homeostasis. GR could also reduce serum fat content in high-fat diet mice, inhibit liver injury, and increase antioxidant mechanism, indicating that GR has hypolipidemia and liver protection activities. MOE water extract can drive vasodilation to reduce arterial blood pressure by stimulating endothelium-derived NO, providing a new method for the treatment of hypertension.[108]

Other effects

Herbs therapy is widely used in the treatment of many diseases due to its low toxicity and good curative effect. Because the therapy affects reproductive physiology and improves certain infertility problems by acting on the hypothalamic–pituitary–gonadal axis.[109] *M. oleifera* is commonly prescribed by herbalists in Nigeria and other tropical countries to treat male infertility and female reproductive diseases.

Traditional plant medicines have often been used for wound treatment since ancient times. Besides the use of chemical drugs, high prices, side effects and other problems, herbal remedies have attracted attention.[110] *M. oleifera* is widely used in wound treatment due to its low side effects and excellent antioxidant and antibacterial activity. In addition to the above functions, *M. oleifera* can also be used for bone protection,[91] promote coagulation[111] and so on.

Mechanism and components of *M. oleifera* in preventing and treating diseases

M. oleifera has been extensively studied for its pharmacological activity and function, and the mechanism of action of *M. oleifera* should be further elucidated at the molecular level. In this paper, from a network pharmacology perspective, we have explored the potential targets and molecular mechanisms of action of the major components of the *Moringa oleifera* leaves (MOL) against major diseases.

Combined with literature review and pharmacological action review results, cancer,[7] hypertension,[112,113] diabetes[93] and arthritis[114] were selected as potential treatment diseases of MOL. Refer to Table 2 for the results of UPLC-Q-TOF-MS analysis of the chemical composition of the MOL.

Metascape data platform was used to analyse the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment of MOL for diabetes, hypertension, arthritis and tumor intersections. The results showed that the main biological processes were icosanoid metabolic process, unsaturated fatty acid metabolic process, fatty acid metabolic process. Molecular functional targets are mainly related to heme binding, tetrapyrrole binding and oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen. The main enrichment items of the targets in cellular component are membrane raft, membrane microdomain and plasma membrane raft.

The enrichment results of KEGG pathway were sorted according to Partition coefficient value ($-\log P$), and the top results were selected to draw a chart ($P < 0.05$)[115] (Fig. 11 and S1 to S4†). The results showed that the arthritis pathway was mainly enriched in: chemical carcinogenesis–DNA adducts, drug metabolism-cytochrome P450, linoleic acid metabolism, *et al.* In collagen-induced arthritis of rats, the linoleic acid metabolic pathway was significantly altered before and after treatment with 2-deoxy-D-glucose, suggesting that the linoleic acid metabolic pathway is closely related to the treatment of arthritis and may serve as a potential target.[116] And studies showed that the bezoar bile acid in the rheumatoid arthritis (RA) rats' body of the small molecule can affect the metabolic pathways of steroid hormone biosynthesis, which led to a decline in immune function in rats, by taking the Atractylodes DC., and the metabolic pathway to normal levels, which can be speculated that by steroid hormones in the treatment of RA.[45]

Study on the major pathways of hypertension has shown that the haploidy insufficiency of glucocorticoid receptor in rats can cause the disorder of linoleic acid metabolism pathway.[57] Another study on the mechanism of melatonin-mediated hypotension, at 18 h, melatonin acted on the (cGMP-PKG) signaling pathway involved in NO synthesis, suggesting that the regulation of blood pressure could be achieved through the cGMP-PKG signaling pathway.[118]

According to KEGG pathway analysis of diabetes, there are drug metabolism-cytochrome P450, linoleic acid metabolism and Neuroactive ligand–receptor interaction, *et al.* Hogan *et al.* used quantitative reverse transcription Quantitative Real-time polymerase chain reaction (QRT-PCR) to identify differentially regulated gene expression of islet amyloid, which is associated with islet physiology and pathology of type II diabetes mellitus, and found that it contains steroidogenic acute regulatory protein (STAR protein), which is part of the synthetic response group of steroid hormone metabolism. It can be inferred that the pathway of steroid hormone metabolism is closely related to diabetes.[119] Resveratrol plays a protective role in the treatment of inflammation-induced vascular injury in type II diabetes by regulating NF-κB signaling pathway, suggesting that this signaling pathway has significant potential for type II diabetes and its complications.[120]

The results of KEGG pathway enrichment analysis suggested that amphiphysin (AMPH1), a protein at the nerve endings, plays an inhibitory role in ovarian cancer. Studies have demonstrated that AMPH1 inhibits the growth of tumor cells by inhibiting the growth of phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling pathway in ovarian cancer.[121] Sadegh *et al.* studied the carcinogenic or anti-cancer effects of miRNA in cancer and apoptosis, and speculated that manipulating miRNA expression level might be a potential method to treat cancer.[122]

Based on the MOL composition-disease target-pathway network, combined with literature records and degree values, the main active components and targets of the MOL for different diseases were screened for molecular docking validation.[123] It is generally believed that the lower the conformational stability energy of the ligand and the receptor, the greater the

possibility of interaction, based on the choice of the degree value of the top core target in the corresponding active ingredient for docking as shown in Fig. S5.† The results show that there is a strong interaction between the target and the compound which score between $-10.5 \sim -9.6$ kcal mol^{-1}. The core compound of arthritis, diabetes and tumour is rutin. The docking results with the lowest binding energies for the four diseases are shown in Fig. S6† respectively.

Preparation formulations of *M. oleifera*

M. oleifera has numerous functions that are expected to be used to treat human diseases. Therefore, the selection of preparation formulation of *M. oleifera* should not be ignored. *M. oleifera* has been developed into granules, tablets, capsules, external preparation and other different preparation formulations such as nanoparticles. Additionally, the ingredient of *M. oleifera* can also be used as preparation excipients in the development of current drugs.

Tablet and capsules

A tablet is a solid preparation of flake or profile-flake formed after uniform mixing of drug and excipient. Commonly, tablets are known to enhance drug dissolution and bioavailability, and has the advantages of stable quality, accurate dose, easy to take and carry. As for the choice of adhesive during the preparation of *M. oleifera* tablet, researchers carried on a detailed study with different adhesives including corn starch, gelatin and microcrystalline cellulose (MCC) and the water extract of *M. oleifera* leaves preparation of tablets, the formula were characterized using various parameters, such as the chemical and physical properties (bulk density tap water content, density ratio, Karr index ash value strength (fragility and crushing strength) and release properties (disintegration and dissolution time tests)).[124,125] The results showed that compared with MCC and corn starch, the tablets with gelatin as binder had the lowest brittleness and disintegration time, and the crushing strength was within the acceptable range (36 kgF). The comprehensive results showed that gelatin was the best adhesive for *M. oleifera* tablets. On the other hand, capsules are composed of is an active content with the appropriate auxiliary materials, either in the hollow hard capsule filling or seal in soft capsule material. *M. oleifera* have bitter taste, is not convenient to make direct oral powder, sealed with hard capsule or hollow capsule material, preparation into capsule not only can hide *M. oleifera* bad smell at the same time also can according to different drug purposes to achieve the location of drug release. *M. oleifera* leaves alcohol extract was prepared and standardized hard gelatin capsules (400 mg per capsule), in order to study the anti-obesity effect of *M. oleifera* leaves.[126] Fifteen female participants aged 45–55 years with a body mass index (BMI) of 29–34 kg m^{-2} were selected for the test. The mean BMI total cholesterol (TC) and lowdensity lipoprotein (LDL) were significantly reduced in obese patients after taking *M. oleifera* capsules for eight weeks ($P < 0.05$). Moreover, *M. oleifera* capsules can also be used as a natural emulsion to increase the volume of breast milk.[127]

New preparation technology

The components of *M. oleifera* have been found to have low solubility bioavailability in drug preparation and poor compliance in common preparations due to their specific smell and taste. To improve the application and promotion of *M. oleifera* preparations, new preparation formulations have been gradually applied in it. Isothiocyanate extracted from *M. oleifera* (MITC) has excellent anti-skin photoaging effect, but its application is limited due to its extremely low water solubility, low bioavailability and easy degradation.[16] Therefore, they prepared amphiphilic hyaluronic acid (HA) conjugated with ceramide (CE) to modify nanoliposomes for MITC (HACE/MITC NPs) delivery. The results showed that the entrapment of MITC in nanoliposomes improves its stability, efficacy, and skin permeation. In addition, *M. oleifera* extract has been found to have mosquito repellent effect and can be used as a safe and cost-effective substitute for *N*,*N*-diethyl-3-methylbenzamide (DEET). Gelatin nanoparticles coated with *M. oleifera* bioactive extract were used to improve its availability.[128] Moreover, silver nanoparticles synthesized from *M. oleifera* leaf extract have also been found to have good anti-leishmania activity.[129] The treated fabric repellency to Culex pipiens mosquitoes showed stable 100% repellency for 6 days for all treated fabrics and ranged from 50 to 90% repellency after 12 days. Green synthesis of silver nanoparticles has been shown to have anticancer activity, Althomali *et al.* took *M. oleifera* leaf extract as the reducing agent and stabilizer of synthesize AgNPs, and the synthesized compound showed superior anticancer activity against human cancer cell line HTC116 and SW480 than *M. oleifera* leaf extract.[130] This result implies that AgNPs synthesized by *M. oleifera* extract could be an ideal strategy to combat colon cancer.

Preparations for external use and others

In order to find a way to prevent 2019-nCoV through personal hygiene, researcher found that various components in *M. oleifera* leaves had antibacterial effects, for example: polyphenols, terpenoids, saponins, and so on.[131] The hand sanitizer is extracted by osmosis, and after processing, it can meet hand sanitizer quality standards and bacteriostatic standards. The hydrogel prepared with hexane extract of *M. oleifera* seeds has significant wound healing activity.[89] *M. oleifera* seed *n*-hexane water gel preparation can be used as a skin repair replacement therapy during wound healing. A membrane consisting of normalized water extract of oil tea leaf was then prepared for wound healing, which enhanced the proliferation and migration properties of human dermal fibroblasts and keratinocytes.[132] Study investigated the potential of *M. oleifera* seed polysaccharide (MOS-PS) and its composite with MOS-PS-AgNPs as an alternative material for wound dressing.[24] In addition, oral treatment of a predominantly Leishmania infected mouse model using silver nanoparticles biosynthesized from *M. oleifera* leaf extract (AG-NPs) was found to significantly reduce the mean size of skin lesions of leishmaniasis.[133] It was proved that the nanoparticles synthesized from *M. oleifera* leaf extract had good anti-leishmania activity.

Pharmaceutical adjunct

Moringa oleifera is available in various dosage forms and due to its diverse composition, it can serve multiple purposes such as an emetic, a dissolvent, an adhesive, and a drug carrier. *M. oleifera* powder, although only slightly soluble in water, has the capability to expand and form a highly viscous solution, which can be used as an adhesive in the preparation of tablets.[134] The coagulated protein was extracted from *M. oleifera*, and its interface properties and interaction with sodium dodecyl sulfate (SDS) were studied. The results showed that the protein extracted from *M. oleifera* seeds had significant surfactant behavior and could be used as a surfactant. Therefore, moringa gum powder extracted from *M. oleifera* can also be used as disintegrating agent. On the basis of the research, moringa gum has potential as a binder and sustained-release agent in tablets.[135] Moreover, *in vitro* drug release studies have evaluated the sensitivity of moringa gum to colonic bacteria and tablets containing it have shown a drug release rate of 90.46%. According to the results, moringa gum could be used as a potential carrier for colonic specific drug delivery.[136]

Future trends

On the one hand, herbal medicine can fully mobilize the human immune system through multi-target and multi-way synergistic effect, and play a radical cure effect. On the other hand, extensive toxicity experiments have proved its safety. Based on this, in recent years, medicinal plants and herbs have gradually become a treatment strategy for a variety of diseases. According to traditional ancient books, *M. oleifera* has multiple functions and plays a key role in curing and preventing diseases. As a medicinal and edible plant, *M. oleifera* has attracted extensive attention from countries around the world. How to study *M. oleifera*, an exotic species, with the help of traditional Chinese medical theory, and explain the pharmacological action and mechanism of its medicinal substance has become an opportunity and challenge for us to face. At the same time, the development of dietary supplements and adjuncts is inextricably linked to the design of prepared formulations, the selection of appropriate preparations, which can improve the stability and safety, in addition, enhance their efficacy. At present, *M. oleifera* only has common dosage forms such as granules, tablets, and capsules. Among the new preparations, only nano preparations have been studied, and the other preparation types are still to be developed. In addition, the development of current preparation types should start from the biopharmaceutical properties of *M. oleifera* itself, such as clarifying the solubility and permeability of relevant medicinal substances. In combination with different dosage forms, such as nano-pharmaceuticals, to improve the safety and stability of the *in vivo* bioavailability of the preparations.

M. oleifera used in health products

Beyond its considerable medicinal properties, *M. oleifera* is also widely utilized in food industry, natural resource preservation efforts, cosmeceuticals and other health product applications. Studies have demonstrated the nutritional benefits of incorporating *M. oleifera* leaves and buds into food products as a rich source of vitamins, minerals, and protein.[137] For instance, adding moringa bud powder (MSP) to conventional pasta has been shown to bolster the content of protein, lipid, fiber and minerals, while the content of carbohydrate showed a trend of decline. The addition of MSP also increases the levels of thiamine, riboflavin, gamma-aminobutyric acid, glucosinolate and antioxidant activity in pasta. Based on the sensory scores, the inclusion of MSP is a technical approach that can improve the nutritional value and biological activity of traditional pasta without compromising consumer acceptance.[138] From the perspective of nutrition, researchers have also developed a cheese product containing *M. oleifera* leaf powder. The aim is to increase the ash, protein, fiber and fat content of the product with the powder, so that cheese can be used as an alternative food in the fight against malnutrition.[139] *M. oleifera* is also widely used in baked goods. In response to consumer demand for organic food, moringa bread was developed by incorporating natural plant moringa leaves into baking product recipes. Studies have found that moringa bread products are more beneficial to human health because they are higher in nutrients and antioxidant activity than regular bread products, which contain less fiber and bioactive substances.[140] Besides, the addition of *M. oleifera* leaf to biscuits can also increase the iron and protein content of the product, while providing essential amino acids to the human body.[141] It is worth noting also *M. oleifera* contains large amounts of flavonoids and phenols, which have good antioxidant activity, so it can be used in the development of cosmeceuticals like body washes and lotions, as it is gentle on skin and helps to reduce irritation. For example, several studies have developed moringa-containing lotions by exploiting the properties of moringa, which can be used externally on the skin and have the properties of natural plant ingredients 64. In addition to its ingredient properties, the addition of *M. oleifera* has the advantage of reducing skin irritation and improving the safety of the body wash.[142] As well as developing excellent emollient products using *M. oleifera* seed oil. Finally, *M. oleifera*'s biocoagulant capabilities make it a promising tool in natural resource management for water purification purposes. *M. oleifera* seed can remove turbidity and natural organic material to bring surface water up to standard requirements and it has the advantages of low-cost, simple operation, high efficiency and health safety.[143]

Summary

M. oleifera is a kind of plant which can be used both as medicine and food. In this review the medicinal component of *M. oleifera* and the chemical components of each component of *M. oleifera* in combination with their functions was summarized, finding that MOL and MOS are currently the most widely used. It was found that the main components of *M. oleifera* are flavonoids and polyphenols. These bioactive compounds exhibit promising antioxidant, anti-inflammatory, anti-tumor, improve gut microbiota antibacterial, neuroprotective antioxidant,

ameliorate metabolic syndrome and other activities. Based on the pharmacological action and molecular mechanism was used to analyse the mechanism of *M. oleifera*, which may play a key role through PI3K-Akt signaling pathway in treating cancer and other diseases. Finally, the application of *M. oleifera* preparation, products and other format is reviewed. However, there are still some key questions that need to be answered through further studies: firstly, as an edible product, it is important to address the bitterness of *M. oleifera* for better future development. Next, although there have been several studies on the composition and function of *M. oleifera*, a more in-depth study of the unique composition, including structural and pharmacological aspects, is needed. Thirdly, the underlying mechanism of the MOL function is obtained from data calculations and simulation methods. To further confirm their correctness, *in vitro* and *in vivo* experiments should be designed for validation. Fourthly, it is found that research on *M. oleifera* preparation formulations mainly focused on traditional tablets, granules and capsules, *etc.* The preparation is relatively monotonous, and how to improve *M. oleifera*'s bitter taste needs further research. In addition, the database used in this study is still constantly updated, so further research is needed to clarify the specific mechanism of *M. oleifera* on diseases, so as to better guide the development of functional foods and complementary drugs.

Abbreviations

M. oleifera	*Moringa oleifera* Lam.
MOL	*Moringa oleifera* Lam. leaves
MOS	*Moringa oleifera* Lam. seed
UPLC-Q-TOF-MS	Ultra High Performance Liquid Chromatography-Quadrupole-Time of Flight-Mass Spectrometry
ROS	Reactive oxygen species
NHDF	Normal human dermal fibroblasts
MOS-PS-AGNPs	Silver nanocomposites with *M. oleifera* seed polysaccharides
IL-6	Interleukin 6
IL-17A	Interleukin 17A
IL-4	Interleukin4
IL-10	Interleukin10
INOS	Inducible Nitric Oxide Synthase
IL-1β	Interleukin1β
NQO1	Quinone oxidoreductase 1
HO-1	Heme oxygenase 1
CAT	Catalase
SOD	Superoxide dismutase
GPX	Glutathione peroxidase
COX-2	Cyclooxygenase-2
A549	Human non small cell lung cancer cell
JAK2	Janus kinase2
STAT3	Signal Transducer and Activator of Transcription 3
PCR	Polymerase Chain Reaction
MSE	*M. oleifera* seed extract
cGMP-PKG	cGMP-dependent protein kinase
MOs-2-a	A polysaccharide separated from *M. oleifera* leaf
DEHP	Di-(2-ethylhexyl) phthalate
Nrf2	Factor erythro2-related factor 2
ER stress	Endoplasmic reticulum stress
NZ	Niazimicin
GSH	Glutathione
MDA	Malondialdehyde
NF-κB	Nuclear factor kappa-B
FA	Fatty acids
AMPK	AMP-activated Protein Kinase
MOLH	*M. oleifera* leaf hydrolysate
GR	1-*O*-(4-Hydroxy-methylphenyl)-α-L-rhamnopyranoside
PPARα	Peroxisome proliferator-activated receptor
mTOR	Mechanistic Target Of Rapamycin
SREBP-1	Sterol regulatory element binding transcription factor 1
GO	Gene ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
−log *P* value	Partition coefficient value
RA	Rheumatoid arthritis
QRT-PCR	Quantitative Real-time polymerase chain reaction
STAR protein	Steroidogenic acute regulatory protein
AMPH1	Amphiphysin
PI3K/AKT	Phosphatidylinositol 3 kinase/protein kinase B
MCC	Microcrystalline cellulose
TC	Total cholesterol
LDL	Lowdensity lipoprotein
MITC	Isothiocyanate extracted from *M. oleifera*
HA	Hyaluronic acid
CE	Conjugated with ceramide
DEET	*N*,*N*-Diethyl-3-methylbenzamide
MOS-PS	*M. oleifera* seed polysaccharide
AG-NPs	*M. oleifera* leaf extract
SDS	Sodium dodecyl sulfate
MSP	Moringa bud powder
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
LPO	Lactoperoxidase
AGEs	Advanced glycation end-products
Bax	BCL_2-associated X protein
BCl_2	B-Cell lymphoma-2
ACE	Angiotensin I-converting enzyme
IL-3	Interleukin-3
STAT5	Signal Transducer and Activator of Transcription 5
UVB	Ultraviolet radiation b
MMP-1	Matrix metalloproteinase 1
MMP-3	Matrix metalloproteinase 3
MMP-9	Matrix metalloproteinase 9
TNF-α	Tumor necrosis factors-α
IAVS	Influenza A viruses
GSK-3β antibody	Glycogen synthase kinase-3β
DDPH	2,2-Diphenyl-1-picrylhydrazyl
ORAC	Oxygen Radical Absorption Capacity

TLR4	Toll-like receptor 4
T-47D	Human breast ductal carcinoma cells
CD31	Platelet endothelial cell adhesion molecule-1
Smac	Second mitochondria-derived activator of caspases
HSP 70	Heat shock protein 70
Skp2	S-Phase kinase-associated protein 2
Fbw7α	F-Box and WD repeat domain-containing7α
INF-κB	Nuclear factor kappa-B inhibitor
ERK	Extracellular-signal-regulated kinase
TGF-β	Transforming growth factor beta
IFN-y	Interferon-gamma
Th2	T-Helper cell type 2
NAFLD	Non-alcoholic fatty liver disease
HFD	Histone fold domain
p^{22phox}	Cytochrome b-245, alpha polypeptide
p^{47phox}	Phospho-Ser359
RUNX2	Runt-related transcription factor 2
COL-1	Collagentypel 1

Author contributions

Xinyue Su, Guanzheng Lu, Liang Ye Maomao Zhu and Xinming Yu collected and analysed the literature data. Xinyue Su and Guanzheng Lu completed the network pharmacology and UPLC-Q-TOF-MS. Xinyue Su and Ruyu Shi was also responsible for writing and submission of this manuscript. Liang Ye and Xinming Yu revised the format of the article. Xinbin Jia, Zhiyong Li and Liang Feng participated in reviewing and proofreading this manuscript. All authors read and approved the final manuscript. All data were generated inhouse, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service or company that could be construed as influencing the position.

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