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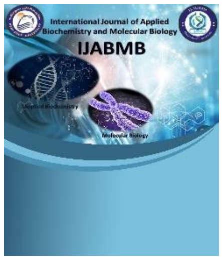

Pharmacological insights into modified citrus pectin: A promising therapeutic potential with anticancer effect

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Running Title: Anticancer and pleiotropic effects of modified citrus pectin

Abstract

Modified citrus pectin (MCP) is a naturally soluble dietary fiber derived from citrus pectin that inhibits galectin-3 (Gal-3), a proinflammatory, profibrotic, and pro-metastatic regulatory protein. Interestingly, the anticancer activity of MCP against multiple cancers, such as colon, prostate, urinary bladder, hemangiosarcoma, and breast cancers, has been demonstrated. It could be attributed to its inhibitory effect on cancer cell growth, prevention of metastasis, and induction of cancer cell apoptosis. In addition, MCP presented protective effects against organ damage in different disease models, including cardioprotective, neuroprotective, renoprotective, and hepatoprotective effects. This could be ascribed to its antioxidant, anti-inflammatory, anti-apoptotic, and antifibrotic effects. Further, immunomodulatory, detoxifying, antimicrobial, and chondroprotective effects have also been demonstrated with MCP. It is available in the market as a regarded safe dietary supplement due to its health-promoting effects. This review involves the interplay between cancer, Gal-3, and MCP, as well as the beneficial impacts of MCP in several models of organ damage.

Keywords: modified citrus pectin, galectin-3, cancer, organ damage

1. Introduction

Citrus pectin was modified to enhance its biological activities and was introduced as modified citrus pectin (MCP). Citrus fiber is obtained from citrus fruits' albedo and membrane parts.[1] Pectin is a complex heteropolysaccharide that consists mainly of two parts: a linear part named the smooth region (homogalacturonan (HG)) and a branched part named the hairy region (rhamnogalacturonan I (RG-I) and rhamnogalacturonan II (RG-II)). This is demonstrated in Figure 1. Pectin occurs primarily as a protopectin characterized by high molecular weight (Mw), gel-like structure, and low solubility, constraining its intestinal absorption and utility in certain fields.[2] Initially, modifying citrus pectin was done at certain temperatures and different pH levels, leading to low Mw and less esterified product, facilitating intestinal absorption into the blood circulation.[3,4] MCP is marketed as PectaSol, prepared by pH-controlled enzymatic treatment, and is available in capsule or powder form. The recommended dose by the manufacturer is fifteen grams to be divided 2-3 times per day and taken with water or juice.[5,6]

The Food and Drug Administration (FDA) of the United States classifies MCP as a generally regarded safe dietary supplement.[7] It is sold as a dietary supplement due to its health-promoting effects, such as heavy metal elimination, antioxidant activity, anti-inflammatory, and hypocholesterolemic effects.[8-10] Moreover, MCP exhibited immunomodulatory effects by increasing proinflammatory cytokines.[11] Further, the anticancer effects of MCP were demonstrated in different preclinical and clinical studies. It inhibits cancer cell growth and prevents metastasis while inducing cancer cell apoptosis.[5,12] Most of the research on MCP focuses on its galectin-3 antagonism.

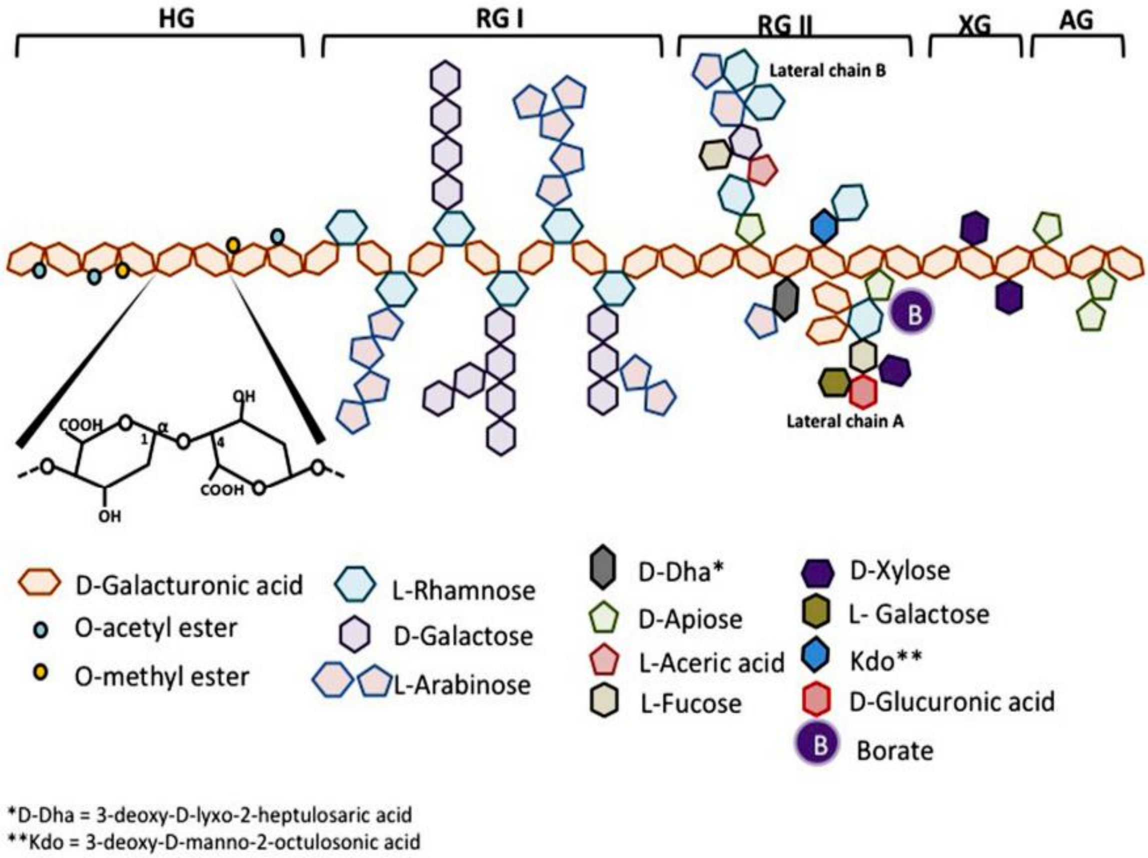

Fig. 1 Schematic illustration of pectin's structure. AG: Arabinogalactan, HG: Homogalacturonan, RG: Rhamnogalacturonan, XG: Xylogalacturonan. Taken, with permission under Creative Commons Attribution License (CC BY), from Anti-cancer activities of pH- or heat-modified pectin.[13]

2. Galectin-3

Galectin-3 (Gal-3) is a multifunctional β-galactoside binding lectin. It is primarily synthesized and secreted by macrophages, eosinophils, and mast cells. It binds to ligands having a β-galactoside structure through its carbohydrate-recognition domain (CRD). Diverse glycosylated matrix proteins, including integrins, fibronectin, and laminin, are among the numerous Gal-3 ligands that have been recognized.[14,15] It is a chimera-type galectin indicated by a monomeric structure that comprises a short N-terminal domain, a C-terminal domain, and an intermediate repeat domain of proline-glycine-alanine-tyrosine[16-18] as shown in Figure 2. Gal-3 has a complicated mechanism of action and remains empirical until now. A possible explanation is that it interacts with many different proteins in the extracellular matrix, inside the cell, at the cell membrane, and in biological fluids. Consequently, it has been documented as participating in numerous physiological and pathological events.[19-22] It is engaged in various biological events, including cell migration, adhesion, apoptosis, angiogenesis, and inflammation. Its pivotal role in tissue fibrosis and inflammation has been documented.[23,24] While Gal-3 has traditionally been viewed as a biomarker linked to disease,[25] recent research has clearly shown its significant role as a therapeutic target for various fibrotic and inflammatory conditions.[26] It is worth noting that the contribution of Gal-3 to the progression and metastasis of cancer has been documented.[27-30]

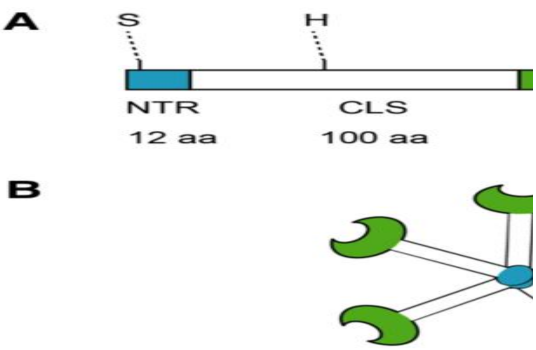

Fig. 2 Structure of galectin-3. (**A**) Galectin-3 protein structure consists of the carbohydrate recognition domain (CRD) of 130 amino acids (aa), which comprises the C-terminal and contains the anti-death motif or Asp-Trp-Gly-Arg (NWGR). The N-terminal Domain (NTD), which has an N-terminal region of 12 amino acids and contains a serine 6 (S) phosphorylation site. (**B**) Pentameric structure of Gal-3.Taken with permission under Creative Commons Attribution License (CC BY) from Galectin-3 in Atrial Fibrillation: Mechanisms and Therapeutic Implications.[31]

The most significant clinical challenge related to cancer is metastasis.

3. Interplay between cancer, Gal-3, and MCP

Metastasis is the dissemination of cancer cells from the primary tumor growth to distant tissues and organs. It is the leading cause of morbidity and death linked to cancer. Regarding the metastatic cascade, Gal-3 and subsequently MCP modulate different rate-limiting steps. MCP is now recognized as an up-and-coming anti-metastatic agent.[12] The initial step undertaken by the cancer cells, after escaping from the primary tumor and undergoing intravasation, is to overcome apoptosis linked to loss of anchorage (anoikis). Gal-3 safeguards cancer cells from anoikis.[32,33] It induces cell cycle arrest at the late G1 phase, which is an anoikis-resistant point.[32] MCP induced apoptosis of human prostatic JCA-1 cells through downregulating cyclin B and cdc2,[34] which may accumulate neoplastic cells in the G2/M phase, consequently inducing apoptosis.[12]

The following rate-limiting step of metastasis entails cancer cell arrest in the microvasculature of the distant organ. Gal-3 has been demonstrated to facilitate the adhesion of metastatic cells to the endothelium.[35-38] Conversely, MCP inhibited their adhesion to endothelium and their homotypic aggregation, which is associated with the arrest of metastatic cells in distant organs and metastatic deposit formation intravascularly.[4,39-41]

Upon infiltrating the microvessels of the target organ, the cancer cells may either undergo proliferation intravascularly till the metastatic tumor surpasses the blood vessel and invades the parenchyma of the distant organ[42] or extravasate before commencing secondary tumor growth. Invasive propensity encompasses a series of interactions between extracellular matrix proteins, related to target organ stroma and basement membrane, and tumor cells mediated by Gal-3.[43] MCP inhibited these Gal-3-mediated interactions. Citrus pectin polysaccharides reduced the invasion of human endothelial cells through the Matrigel dose-dependently,[40] as well as that of human metastatic buccal carcinoma and MDA-MB-231 human breast carcinoma metastatic cells.[44]

Following the first parking in distant organs and extravasation, almost all cancer cells experience apoptosis triggered by different factors, and less than 2% survive and cause micrometastasis.[45] Consequently, one of the most critical rate-limiting steps influencing metastasis efficacy is the clonogenic survival of early metastatic colonies. It was described that Gal-3 is important in neoplastic cell clonogenic survival through its anti-apoptotic effects, working on the mitochondrial apoptosis pathways.[46-48] Some reports indicated that MCP-induced Gal-3 blockade could antagonize the anti-apoptotic effects of Gal-3, hence decreasing cancer cells' clonogenic survival.[48] Accordingly, MCP hindered the hemangiosarcoma cells' clonogenic survival in a dose-dependent way, increasing the apoptosis of tumor cells.[49]

As micrometastases become clinically significant secondary tumors, angiogenesis is essential for blood vessel development. A close relationship exists between Gal-3 and the morphogenesis of endothelial cells and angiogenesis.[50-52] It was shown that Gal-3 behaves as a potent angiogenic factor through endothelial chemoattraction and cell motility induction, Matrigel invasion, and capillary tube formation.[40,50] It was confirmed that MCP halted the angiogenic activity of Gal-3. In a dose-dependent way, MCP inhibited human endothelial cells' chemotaxis towards Gal-3, and it also inhibited endothelial cell capillary tube formation in vitro.[50] Further, it decreased spontaneous metastasis and angiogenesis when given to tumor-bearing mice.[50]

MCP can influence chemoresistance. Most anticancer agents work by inducing tumor cell apoptosis through the mitochondrial apoptosis pathway.[53] Gal-3 mitigates this pathway [54]. As a result, Gal-3 was demonstrated to directly modulate the cancer cell sensitivity to chemotherapeutic agents, for example, staurosporine,[54] cisplatin,[54,55] bortezomib,[56] etoposide,[55] doxorubicin,[49] and dexamethasone.[56] Thus, MCP as a Gal-3 blocker may significantly affect the sensitivity of cancer cells to chemotherapy by limiting the anti-apoptotic effects of Gal-3 on the mitochondrial apoptosis pathway. The inhibition of anti-apoptotic effects of Gal-3 by MCP was shown to be adequate to augment the response of multiple myeloma cells to dexamethasone-induced apoptosis and to reverse their resistance to bortezomib.[56] Upon MCP intervention on hemangiosarcoma cells, their sensitivity to doxorubicin-induced apoptosis was significantly elevated.[49]

It was demonstrated that MCP not only enhances anticancer drug-induced apoptosis but also induces cancer cell apoptosis by itself. MCP induced apoptosis via the caspase-8-to-caspase-3 pathway in multiple myeloma cells, notably without substantial alterations in mitochondrial membrane potential.[56]

The anticancer activity in different reports continues. A previous study reported that Gal-3 stimulated the activation of signal transducer and activator of transcription 3 (STAT3); its constitutive activation in ovarian cancer cells is related to chemoresistance. Moreover, paclitaxel and MCP combination showed synergistic cytotoxicity with decreased cell viability and elevated caspase-3 activity in human SKOV-3 ovarian cancer cells.[57] Another study showed that MCP synergized with paclitaxel against SKOV-3 multicellular tumor spheroids by inhibiting STAT3 activation, decreasing its downstream target hypoxia-inducible factor-1α (HIF-1α), lowering integrin mRNA levels, and consequently reducing protein kinase B activity.[58]

MCP enhanced the cytotoxicity of ionizing radiotherapy in a prostatic cell line (PCa) by decreasing anti-apoptotic Gal-3, elevating reactive oxygen species formation, and modulating DNA repair pathways. Moreover, MCP inhibited the PCa metastatic phenotype through Gal-3 blockade.[59] Furthermore, the MCP and doxorubicin combination resulted in progressive cytotoxicity in prostate cancer cell lines, leading to cell death mediated by cell cycle arrest in

LNCaP and apoptosis in DU-145.[60] MCP-induced cytotoxicity of androgen-dependent and -independent prostate cancer cell lines may be partly due to mitogen-activated protein kinase signaling inhibition and caspase-3 activation.[61] Furthermore, MCP synergistically diminished the invasive metastatic behavior of highly metastatic human prostate and breast cancer cells *in vitro* when combined with prostate or breast polybotanical health supplements, respectively.[62] Additionally, MCP-induced Gal-3 blockade inhibited tumor-associated macrophages (TAMs) induced breast cancer progression and metastasis in hypoxia; hypoxia elevates the formation and secretion of Gal-3 from TAMs.[63]

It was evident that MCP decreased the growth of colon tumors that were implanted in mice.[33] In a previous *in vitro* study, MCP blocked extracellular Gal-3-induced human colon cancer cell migration at which Gal-3 binds to epidermal growth factor receptor, inducing colon cancer cell migration.[64] Moreover, MCP inhibited liver metastasis in colon cancer in mice through Gal-3 inhibition.[65]

It has been shown that MCP-mediated Gal-3 inhibition decreased urinary bladder cancer proliferation and survival through apoptosis induction and cell cycle arrest *in vivo* and *in vitro*.[66]

In blood cultures, MCP significantly activated natural killer cells and T-helper cells. Additionally, natural killer cells exhibited functionality against K562 leukemic cells. It appears that the MCP immunostimulatory carbohydrates consist of low-Mw pectin polymer rich in unsaturated and saturated oligo-galacturonic acids, as well as a low degree of methyl esterification [67]. It is worth noting that MCP enhanced the cytotoxic activity of methotrexate both in choriocarcinoma (JEG3) and acute lymphoblastic leukemia (Nalm6) cell lines.[68]

The anticancer activity of MCP is affected by its size and domain structures. Using autoclaving for MCP production, enriching de-esterified HG oligomers, and reducing RG-I and arabinogalactans-I (AG-I) in MCP lower than 3 KDa, or decreasing RG-I and increasing AG-I in MCP between 10-30 KDa led to anticancer activity by inhibiting cancer cell migration, proliferation, and aggregation.[69] MCP is ideal as an adjunctive immune and oncological therapy with its low esterification degree, low Mw, and high RG-II domain percentage.[70]

Different clinical trials have demonstrated the potential anticancer effects of MCP. A phase II open-labeled pilot study assessed patients with prostate cancer, untreated at baseline, with low prostate-specific antigen (PSA) (<10 ng/ml) but gradually rising. MCP was administered daily for 12 months at a dose of 18 capsules (14.4 g). In 70% of patients, PSA doubling time was prolonged. These results suggest a slower progression of cancer and possible life extension.[71] An initial pilot trial examined 7 prostate cancer patients (PSA ranges 0.63-7.5) who had relapsed or failed previous therapy. The daily MCP dose was 15 g. Four of seven patients had a positive response (>30% PSA doubling time prolongation), one had a stable state, one had a partial response, and one did not. Three years of survival were observed in all patients.[72] A phase II open-labeled study assessing non-metastatic biochemically relapsed prostate cancer in thirty-four patients who administered 4.8 g of MCP three times daily for 6 months. Six patients experienced grade 1 side effects (bloating and gas), but no patient experienced grade 3 or 4 toxicity. Stable or decreased PSA with negative scans was observed in 21 patients. Moreover, stable or improved PSA doubling time with no metastasis on scans was observed in 27 patients.[73] After this initial six months of MCP, a second long-term treatment for 12 months with patients exhibiting no disease progression was performed. After MCP therapy for 18 months, 90% (n=35) showed improved PSA doubling time, and all presented negative scans. No one exhibited grade 3 or 4 toxicity, and consequently, MCP exhibits sustained long-term safety and efficacy in biochemically relapsed prostate cancer.[74]

Patients suffering from solid tumors at an advanced stage were examined in an open-label clinical trial. Each treatment cycle consisted of eight weeks of daily administration of 15 g MCP. 20.7% (6 of 29 patients) experienced clinical benefits and improved quality of life. After 2 cycles, 22.5% (11 of 49 patients) exhibited a stable disease, and 12.3% (6 of 49 patients) had a stable disease for over 24 weeks. One metastasized prostate cancer patient had a 50% reduction of serum PSA levels after sixteen weeks of therapy, along with enhanced quality of life, clinical benefit, and pain relief.[75]

4. Protective effects of MCP on experimental and clinical studies

The protective effects of MCP were evidenced in several disease models, which are summarized in Table 1.

4.1. *Cardiovascular effects*

A previous study reported that MCP ameliorated heart fibrosis elicited by isoproterenol in rats through inhibition of the Gal-3/TLR-4 (toll-like receptor-4)/NF-κB (nuclear factor kappa B) signaling pathway, thereby reducing the cardiac levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-18, and interleukin-1β (IL-1β), implicating in heart failure pathogenesis.[76] Moreover, MCP protected against isoproterenol-caused cardiac hypertrophy in rats through activation of p38 signaling and blocking Gal-3/TLR-4/JAK2 (Janus kinase 2)/STAT3 signaling pathway.[77] Recently, MCP showed protective effects against isoprenaline-caused myocardial infarction through Gal-3 inhibition, restoring echocardiographic parameters, and protection against cardiac remodeling.[78] Additionally, MCP-induced Gal-3 inhibition protected against isoproterenol-elicited left ventricular dysfunction and fibrosis.[79] MCP prevented cardiac alterations related to ischemic reperfusion (IR) injury. It attenuated cardiac fibrosis and inflammation in the rats' left ventricles and protected against extracellular matrix remodeling through Gal-3 inhibition.[80] Also, MCP mitigated heart and kidney fibrosis and dysfunction in an animal model of hyperaldosteronism through Gal-3 blockade.[81] In hypertensive rats with hyperaldosteronism, MCP reversed vascular inflammation, hypertrophy, and fibrosis through Gal-3 inhibition.[82] MCP-mediated Gal-3 inhibition protected against cardiac lipotoxicity in obese rats, identified by decreasing total triglycerides, lysophosphatidylcholine levels, and reactive oxygen species.[83] MCP-caused Gal-3 inhibition facilitated the upregulation of peroxiredoxin-4, thereby decreasing cardiac oxidative stress in doxorubicin-caused cardiotoxicity in rats.[84] As mentioned previously, MCP inhibited Gal-3/TLR-4/NF-κB signaling in a rat model of arteriogenic erectile dysfunction, reducing inflammation, fibrosis, and endothelial injury.[85] Most recently, MCP protected against aortic dissection through inhibiting Gal-3/TLR-4 signaling and blocking pyroptotic macrophage-induced inflammation.[86]

4.2.Renoprotective effects

The MCP's anti-apoptotic and anti-fibrotic effects were mediated through Gal-3 blocking in cisplatin-evoked kidney damage in mice.[87] It exhibited renoprotective effects in folic acid-induced acute renal damage in mice through Gal-3 inhibitory, anti-apoptotic, anti-inflammatory, and antifibrotic impacts.[88] Further, in spontaneously hypertensive rats, MCP had Gal-3 inhibitory, antifibrotic effects, and anti-inflammatory properties. It reduced the levels of inflammatory mediators, including Cd80, Cd68, Cd44, Cd45, osteopontin, and chemoattractant protein-1, in addition to fibrotic markers, TGF-β, and collagen type I.[89] Moreover, in two models of normotensive rats, MCP ameliorated mild renal injury induced by either aortic stenosis or obesity via

Gal-3 inhibition, which offered anti-inflammatory and antifibrotic effects.[90] Recently, MCP ameliorated oxidative stress, fibrosis, inflammation, and apoptosis beyond its glycemic control against type-2 diabetes mellitus-elicited nephropathy in mice.[74]

4.3.Hepatoprotective effects

By preventing fibrosis and apoptosis in rats exposed to carbon tetrachloride (CCL4), MCP demonstrated hepatoprotective effects via Gal-3 inhibitory effects.[91] It was recently demonstrated that MCP protects against methotrexate-caused liver and pulmonary damage in rats through antioxidant effects, identified by decreased malondialdehyde (MDA) levels, increased superoxide dismutase (SOD) activity, nuclear factor erythroid 2 related-factor 2 (Nrf2), and reduced glutathione levels, anti-inflammatory effects, mediated by the blockade of Gal-3/TLR-4/NF-κB pathway, antifibrotic effects, mediated by Gal-3 inhibition, reduced collagen and TGF-β levels, and antiapoptotic effects.[68]

4.4.Neuroprotective effects

Through Gal-3 blockade, MCP protected against post-subarachnoid hemorrhage-induced disruption in the blood-brain barrier in mice, with mechanisms that may involve TLR-4 and extracellular signal-related kinase 1/2 (ERK 1/2), STAT3, and metalloproteinase-9 (MMP-9) in activation.[92] It was reported that *in vitro* and *in vivo* models of diabetes-induced cognitive impairment, MCP offered antioxidant effects, indicated by reduced levels of MDA and increased activity of SOD and glutathione peroxidase, and anti-inflammatory effects, demonstrated by Gal-3 inhibition and decreased levels of proinflammatory cytokines such as TNF-α, IL-1β, and interleukin-6.[93] Previous experimental investigations uncovered the neuroprotective effects of MCP against ischemic stroke via inhibiting Gal-3/TLR-4/NF-κB/NLRP-3 (NOD-like receptor 3)/cleaved caspase-1/IL-1β signaling pathway in microglia.[94] It mitigated cognitive deficits and neuroinflammation by blocking Gal-3 in addition to its antioxidant potential in scopolamine-induced Alzheimer's in rats.[95]

4.5. Detoxifying effects

It was proved clinically that the urinary excretion of cadmium, arsenic, and lead is increased by MCP in healthy subjects.[96] In 5 case reports, MCP decreased levels of heavy metals with no side effects when administered alone or in combination with alginates.[97] In hospitalized children with lead toxicity, MCP safely decreased the serum level of lead and increased its level in urine.[10] Furthermore, MCP/alginate supplementation enhanced the excretion of uranium in feces with no side effects in a family exposed chronically to uranium in their environment and diet.[98]

4.6. Miscellaneous effects

Of note, MCP had protective effects against articular cartilage defects in rabbits through Gal-3 inhibitory, anti-inflammatory, and antidegenerative effects.[99] Further, it showed synergistic effects with hyaluronate against osteoarthritis in rabbits through modulating metabolic and inflammatory processes and consequently alleviating the progression of osteoarthritis.[100] Both MCP and Honokiol (HNK) showed antioxidant and anti-inflammatory effects when explored *in vitro*. MCP showed a higher antioxidant effect than HNK in a dose-dependent way. Of note, they demonstrated higher synergistic antioxidant and anti-inflammatory effects upon combination. This was evidenced by inhibiting lipid peroxidation, NF-κB, and cyclooxygenase-II.[9] Additionally, the immunomodulatory effects of MCP were identified in the mouse spleen, which elevated the levels of proinflammatory cytokines, which could be advantageous in immunotherapy.[11]

Coadministration of MCP with probiotic supplement *Lactobacillus acidophilus* ATCC 4356 improved intestinal microbiota population and integrity. There was a significant elevation in fecal lactobacilli number in MCP alginate probiotic-challenged mice.[101] It was previously reported that the adhesion of *Escherichia coli,* which produces toxins, and the cytotoxicity of Shiga toxin were decreased by MCP.[102] MCP exhibited antimicrobial activity against *Staphylococcus aureus* (MRSA) *in vitro*. In addition, it showed additives, with most of the MRSA strains, and synergetic, with two MRSA strains, effects when combined with cefotaxime.[103]

Table 1: Protective effects of modified citrus pectin on experimental and clinical studies

Effect	Disease model	Outcomes summary
Cardioprotective effect[76]	Isoproterenol-induced heart failure in rats	MCP inhibited the Gal-3/TLR-4/NF-κB signaling pathway. It decreased the expressions of IL-18, TNF-α, and IL-1β
Cardioprotective effect[77]	Isoproterenol-caused cardiac hypertrophy in rats	MCP activated p38 signaling and blocked Gal-3/TLR-4/JAK2 pathway
Cardioprotective effect[78]	Isoprenaline-caused myocardial infarction in type-2 diabetes mellitus rats	The echocardiographic parameters were restored with MCP. Further, it inhibited Gal-3 in parallel to its protective effect against cardiac remodeling

Cardioprotective effect[79]	Isoproterenol-elicited left ventricular dysfunction and fibrosis in mice	MCP inhibited Gal-3, which protected against isoproterenol-elicited left ventricular dysfunction and fibrosis
Cardioprotective effect[80]	Ischemia-reperfusion-induced myocardial injury in rats	MCP blocked Gal-3, concomitant with reduced cardiac inflammation and fibrosis. It decreased the ischemic area and extracellular matrix remodeling
Cardioprotective effect[83]	Cardiac lipotoxicity in high-fat diet-induced obesity in rats	MCP blocked Gal-3, which mediated a decrease in total triglycerides, phosphatidylcholine levels, and reactive oxygen species
Cardioprotective effect[84]	Doxorubicin-caused cardiotoxicity in rats	MCP upregulated peroxiredoxin-4 through Gal-3 inhibition and therefore decreased oxidative stress
Vascular protective effect[82]	Aldosterone-caused vascular fibrosis in rats	MCP reversed vascular inflammation, hypertrophy, and fibrosis, identified by reducing collagen type I content, through Gal-3 inhibition
Vascular protective effect[85]	High-fat diet-induced arteriogenic erectile dysfunction in rats	MCP inhibited Gal-3/TLR-4/NF-κB signaling. It decreased levels of TNF-α, IL-6, TGF-β, and collagen type I
Vascular protective effect[86]	β-aminopropionitrile fumarate/angiotensin-II induced aortic dissection in mice RAW264.7 cells treated with H_2O_2 (*In vitro*)	*In vivo*, MCP decreased the mortality and incidence of aortic dissection. It reduced the infiltration of inflammatory cells into the aorta. Additionally, it blocked Gal-3/TLR4 signaling

		In vitro, MCP ameliorated pyroptosis and macrophage death induced by H_2O_2
Cardio-renoprotective effect[81]	Aldosterone-induced heart and kidney injuries in rats	MCP inhibited the aldosterone-induced increase in blood pressure, cardiac remodeling, and fibrosis. It lowered TGF-β and collagen type I. Also, it abrogated aldosterone-induced hyperfiltration, albuminuria, kidney and glomerular hypertrophy, tubular lesions, and renal fibrosis.
Renoprotective effect[87]	Cisplatin-evoked kidney damage in mice	MCP blocked renal Gal-3, which led to suppression of protein kinase α, apoptosis, cleaved caspase 3, collagen type I, and fibronectin.
Renoprotective effect[88]	Folic acid-induced acute renal damage in mice	MCP reduced renal proliferation in the acute phase of folic acid-induced acute renal damage. It decreased the levels of Gal-3, TGF-β, collagen type I, fibronectin, α-SMA, IL-1β, and TNF-α in the injury recovery phase.
Renoprotective effect[89]	Spontaneously hypertensive rats	MCP inhibited Gal-3. It reduced the levels of inflammatory mediators, including Cd80, Cd68, Cd44, Cd45, osteopontin, and chemoattractant protein-1, in addition to fibrotic markers, TGF-β, and collagen type I.
Renoprotective effect[90]	Two models of renal damage in normotensive rats induced by either aortic stenosis or obesity	In the obesity model, MCP blocked Gal-3, decreased TGF-β and collagen type I as fibrotic markers, normalized α-SMA and E-cadherin as EMT markers, decreased osteopontin as an inflammatory marker,

		and ameliorated the kidney injury molecule 1. In the aortic stenosis model, MCP blocked Gal-3, decreased connective tissue growth factor, TGF-β, and collagen type I, normalized α-SMA, E-cadherin, fibronectin, and β-catenin, reduced osteopontin, and ameliorated the kidney injury molecule 1 and NGAL
Renoprotective effect[74]	Type-2 diabetes mellitus-elicited nephropathy in mice	MCP decreased MDA levels, elevated catalase activity, and GSH levels. It reduced iNOS, TGF-βRII, TNF-α, and caspase-3 levels.
Hepatoprotective effect[91]	Carbon tetrachloride-induced liver fibrosis	MCP inhibited Gal-3. It decreased fibrosis markers, α-SMA, TIMP-1, and collagen type I. Moreover, it reduced MDA levels and increased GSH content and SOD activity. It mediated the activation of hepatic stellate cells and apoptosis induction.
Hepato- and pulmonary protective effects[68]	Methotrexate--caused liver and pulmonary damage in rats	Both in liver and lung tissues, MCP decreased MDA levels, increased SOD activity, Nrf2, and GSH levels. It blocked Gal-3/TLR-4/NF-κB pathway and reduced collagen and TGF-β levels, and cleaved caspase-3
Neuroprotective effect[92]	Post-subarachnoid hemorrhage-induced disruption of the blood-brain barrier in mice	MCP inactivated TLR-4 and ERK 1/2, STAT3, and MMP9 through Gal-3 blockade.

Neuroprotective effect[93]	Diabetes-induced cognitive impairment *in vivo* in rats and *in vitro* in microglia cells	MCP blocked Gal-3, reduced MDA levels, increased activity of SOD and glutathione peroxidase, and decreased levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6
Neuroprotective effect[94]	Cerebral ischemia reperfusion in mice as an *in vivo* model Oxygen-glucose deprivation/ reoxygenation in microglia and neuronal cells as *in vitro* models	MCP ameliorated cerebral cortex cell injury and decreased infarct volume, cerebral water content, and scores of neurological deficits in mice. Moreover, it reduced apoptosis and increased cell viability in neuronal cells. It inhibited Gal-3/TLR-4/NF-κB/NLRP-3/cleaved caspase-1/IL-1β signaling pathway in microglia
Neuroprotective effect[95]	Scopolamine-induced Alzheimer's in rats	MCP decreased Gal-3, IL-6, and TNF-α, elevated brain-derived neurotrophic factor and SOD activity, and enhanced the memory performance.
Chondroprotective[99]	Articular cartilage defects in rabbits	MCP decreased levels of Gal-3, MMP13, IL-1β, Collagen 1A2 and inhibited cartilage degeneration
Chondroprotective[100]	Osteoarthritis in rabbits	MCP and hyaluronate combination alleviated the signs and symptoms of osteoarthritis, protected against the degeneration of articular cartilage, and reduced synovial inflammation.
Detoxifying effect[96]	Metal toxicity (clinical trial)	MCP increased the urinary excretion of cadmium, arsenic, and lead in healthy subjects

Detoxifying effect[97]	Metal toxicity (clinical trial)	MCP decreased levels of heavy metals with no side effects when administered alone or in combination with alginates
Detoxifying effect[10]	Lead toxicity in hospitalized children	MCP safely decreased the serum level of lead and increased its level in urine
Detoxifying effect[98]	Low-level chronic exposure to uranium	MCP/alginate supplementation enhanced the excretion of uranium in feces with no side effects
Immune function[9]	Inflammation (*in vitro*)	The MCP and Honokiol combination demonstrated higher synergistic antioxidant and anti-inflammatory effects, inhibiting lipid peroxidation, NF-κB, and cyclooxygenase-II.
Immune function[101]	Probiotic	There was a significant elevation in fecal lactobacilli number in MCP alginate probiotic-challenged mice
Antimicrobial effect[103]	*Staphylococcus aureus* (*In vitro*)	MCP had antimicrobial activity alone or upon combination with cefotaxime, additive and synergistic effects, against *Staphylococcus aureus*

Abbreviations: α-SMA: Alpha smooth muscle actin, EMT: Epithelial-mesenchymal transition, ERK: Extracellular signal-related kinase, Gal-3: Galectin-3, GSH: reduced glutathione, IL: Interleukin, iNOS: inducible nitric oxide synthase, JAK2: Janus kinase 2, MCP: Modified citrus pectin, MDA: Malondialdehyde, MMP: Metalloproteinase, NF-κB: Nuclear factor kappa B, NGAL: Neutrophil gelatinase-associated lipocalin, NLRP-3:NOD-like receptor 3, Nrf2: Nuclear factor erythroid 2 related-factor 2, SOD: Superoxide dismutase, STAT3: Signal transducer and activator of transcription 3, TGF-βRII: Tumor growth factor β receptor II, TGF-β: tumor growth factor beta, TIMP-1:

Tissue inhibitor metalloproteinase 1, TLR-4: toll-like receptor-4, TNF-α: Tumor necrosis factor alpha.

5. Conclusion

Several benefits of MCP have been highlighted in both preclinical and clinical studies. It showed antioxidant, antifibrotic, anti-inflammatory, and anti-apoptotic effects mediating its protective effects in different disease models. Moreover, its anticancer activity is documented. It inhibits tumor cell growth and metastasis. As a natural Gal-3 inhibitor, MCP can be combined with other chemotherapeutic agents as a chemosensitizer or even to protect from chemotherapy-associated adverse effects, but these applications warrant clinical studies to evaluate its effectiveness, appropriate doses, and safety profile before clinical applications.

6. Conflict of Interest

The authors have declared that no competing interests exist.

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8. Authorship contribution statement

Randa Ismail drafted the manuscript, while **Gehan H. Heeba** contributed to its conceptualization and reviewing. **Heba A. Habib, Aliaa F. Anter** critically reviewed the manuscript, and all approved its final version

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