Journal of Applied Pharmaceutical Science Vol. 0(00), pp 001-013, 2024
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2024.171645
ISSN 2231-3354

Biological activities of *Chrysanthemum morifolium* and *Chrysanthemum indicum*: Molecular prospective

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ARTICLE HISTORY

Received 02/10/2023
Accepted 23/04/2024
Available Online: XX

Key words:
Chrysanthemum, anti-inflammatory, antioxidant, anticancer, silver nanoparticles.

ABSTRACT

Chrysanthemum is an edible flower from a member of the Asteraceae family recognized for its wide variety of therapeutic benefits. The use of natural products as supplemental therapy has expanded dramatically due to the notion that they have fewer side effects. This current review attempts to summarise both *Chrysanthemum morifolium* and *Chrysanthemum indicum* health benefits and the molecular underpinnings of their biological effects with the addition of their recent use in green nanotechnology applications. Using PubMed and Scopus from 2008 to 2022, a literature search was done for relevant material addressing the biological activities of *C. morifolium* and *C. indicum*. Chrysanthemum's anti-inflammatory, antioxidant, anticancer, anti-diabetic/anti-obesity, and antibacterial properties have been investigated. Both Chrysanthemum has been found to possess the ability to decrease pro-inflammatory proteins and genes, initiate apoptosis in cancer cells as well as modulate lipid metabolism to mitigate the development of obesity and diabetes. Moreover, it has been demonstrated that Chrysanthemum has antioxidant characteristics, thereby safeguarding against oxidative harm through the activation of cytoprotective and antioxidant genes. In addition, findings also demonstrated the green synthesis of silver nanoparticles from Chrysanthemum exhibits antimicrobial properties. Notably, no deleterious effects were seen following oral administration of both extracts in vivo. As demonstrated by preclinical investigations, the favorable effects of Chrysanthemum treatment need to be confirmed by more research or clinical trials.

INTRODUCTION

Chrysanthemum is a well-known genus comprising almost 300 species distributed around the world. Several of these species are cultivated as ornamental plants in gardens, while some exist as herbs and under shrubs. A total of 40 species of Chrysanthemum are mainly found in East Asia and belong to the Asteraceae family [1,2]. Studies reported that the entire plant carries therapeutic abilities, and the prominent components can be found mainly in its flower. Traditionally, due to its wide range of beneficial uses, Chrysanthemum is commonly consumed in drinks and medicine. For example, Chrysanthemum flowers were dried and used as herbal tea in North-eastern Asia, such as China and Korea. It reportedly treats several illnesses, such as headaches, inflammation, hypertension, cholera, respiratory disease, and other related diseases [3,4]. The therapeutic effect of Chrysanthemum has been clinically proven for decades based on its medicinal history. According to the World Health Organization (WHO), plant-based pharmacological drugs are now preferred as the safest medication because they are practical and exhibit less toxicity than modern drugs.

Chrysanthemum morifolium and *C. indicum* are perennial herbs with aromatic alternate, lobed, or serrated leaves. Numerous recent studies demonstrated that extracts or monomeric compounds from both plants have a variety of pharmacological activities. Studies have shown that flavonoids and phenolic acids are major components of secondary metabolites essential to exert therapeutic activities in Chrysanthemum species [5,6]. Identification of phytochemical

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content from *C. indicum* isolated around 191 natural compounds, including 42 flavonoids, 96 terpenoids, 21 phenylpropanoids, phenolic acids, 12 spiro ketones, and others [5,6]. Likewise, a previous study also discovered that *C. morifolium* yielded 60 flavonoid compounds when isolated using column chromatography, most of which were glycosidic derivatives of luteolin, apigenin, acacetin, diosmetin, or eriodictyol in the C7 position [7]. Extracts from *C. morifolium* and *C. indicum* can be found in different parts of the Chrysanthemum, such as flowers, aerial parts, or whole herbs. Detection of active compounds, especially with a high level of flavonoid in Chrysanthemum, may lead to understanding how these edible flowers exerted their pharmacological effects.

Detailed discussions on the pharmacological properties and pathways of the Chrysanthemum species are limited. This current review discusses and summarizes the health benefits of two main species of Chrysanthemum: *morifolium* and *indicum*. The underlying molecular mechanisms that govern the beneficial effects are also highlighted. Hence, the current review provides additional information to researchers about the therapeutic potential for broadening the use of Chrysanthemum extract.

LITERATURE SEARCH

An updated overview of the pharmacological activities of Chrysanthemums, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and antidiabetic/anti-obesity properties, as well as their underlying mechanisms of action, are presented in this review. A literature search was performed on PubMed and Scopus using the keywords "*C. morifolium*" or "Chrysanthemum indicum" and "anticancer," "antimicrobial," "antioxidant," "anti-inflammatory," "anti-obesity," or "antidiabetic" published between 2008 and 2022. Original research articles on the health effects of Chrysanthemum published in English were included.

PHARMACOLOGICAL POTENTIAL OF CHRYSANTHEMUM

Anti-inflammatory

Living cells constantly produce free radicals, and a healthy immune system requires moderate concentrations of these molecules. Excessive production of free radicals subset from endogenous (primarily mitochondrial) and exogenous (environmental pollution) sources would harm cells, leading to oxidative stress and further activating the inflammatory response in cells [8]. Cellular inflammation that persists for an extended period becomes chronic inflammation, which is the cause of numerous diseases. Lipopolysaccharides (LPS)-induced RAW264.7 cells are frequently used as a model to study anti-inflammation as they form a complex ligand with toll-like receptor (TLR) 4 to induce specific signaling pathways in regulating the inflammatory gene expression [9]. In the mice model of LPS-induced acute lung injury, many pro-inflammatory cytokines of tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels were released, indicating macrophage activation. Treatment with *C. morifolium* at 50, 100, and 200 mg/kg significantly reduced these pro-inflammatory markers while increasing the tumor growth factor (TGF)-β1 and IL-10 as a compensatory anti-inflammatory response [10]. Maintaining normal physiological homeostasis requires a balance between pro-inflammatory and anti-inflammatory components, suppressing oxygen free radicals. Similarly, in mice models of Cisplatin-induced acute kidney injury, supplementation with *C. morifolium* reduced the anti-cancer drug's toxicity by blocking the inflammatory pathway via inhibition of the monocyte chemoattractant protein-1 production [11]. Inhibition of reactive oxygen species (ROS) generation, messenger RNA (mRNA) expression of IL-1β, IL-6, IL-8, and TNF-α suggest regulating the inflammatory responses by *C. morifolium* [12].

In another study, administration of *C. indicum* at 200 mg/kg intraperitoneal inhibited the activity of IL-1, TNF-α, and the accumulation of leukocytes in both acute and chronic skin inflammation of mouse models [13]. Wu *et al*. explored the anti-inflammatory effects of Chrysanthemum in an inflammation animal model by xylene-induced mouse ear edema. Supplementation of *C. indicum* at 40, 80, and 120 mg/kg dose-dependently decreased the inflammatory response of the edema paw significantly at 2 to 6 hours [14]. A study showed that multiple pro-inflammatory cytokines are highly produced during the late stages of edema (2–6 hours), which may exacerbate the inflammatory response [15]. Significant reduction in the production of inducible nitric oxide (NO) synthase and cyclooxygenase-2 (COX-2) inflammatory factors suppressed the production of IL-6, TNF-α, IL-1□, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF--B). It is well known that COX-2 and iNOS expression levels are highest in the late stages of carrageenan-induced paw edema [16]. Findings also revealed that the anti-inflammatory effect of *C. indicum* is related to disinhibition prostaglandin (PGE)-2 and NO syntheses, which play a central role in inflammatory responses. Likewise, other findings demonstrated that oral *C. indicum* at 42.5, 85, and 170 mg/kg significantly inhibit carrageenan-induced paw edema. Treatment also up-regulated the level of IL-1β while down-regulated PGE-2, mediating the inflammatory response acting at an appropriate level [17]. Vasodilatation inhibition effect in the early stage of acute inflammation response, endowing *C. indicum* treatment a promising potential for anti-inflammation via decreasing the inflammatory mediator release.

Interestingly, the synergistic effect of *C. indicum* attenuated the anti-tumor drug bleomycin-induced pulmonary fibrosis by reducing pro-inflammatory cytokines of IL-6 and TNF-α production [18]. *Chrysanthemum indicum* exhibits stronger anti-inflammatory activity via inhibiting pro-inflammatory mediators of IL-1, IL-6, and TNF-α [19]. In addition, *C. indicum* reduced inflammatory mediator NO and pro-inflammatory cytokines (IL-1β and IL-6) levels in LPS-stimulated RAW264.7 macrophages. Decreased expression levels of antigen-presenting surface markers like major histocompatibility complex-II and CD80 were also observed [20]. Activated macrophages secrete pro-inflammatory cytokines that stimulate numerous cell signaling pathways to promote inflammation. A decrease in the release of pro-inflammatory cytokines evidences the ability of Chrysanthemum extracts to control inflammation. Further investigations

revealed that *C. indicum* possesses anti-inflammatory effects via hyperproliferation suppression and apoptosis induction in IL-6/sIL-6R-stimulated rheumatoid arthritis fibroblast-like synoviocytes [21]. Targeting the specific blockade of IL-6-regulated signaling pathways may lead to a promising approach for treating diseases since high levels of IL-6/sIL-6R have been reported in several chronic inflammatory conditions [22]. The extracts suppressed the production of TNF-α, IL-1, and IL-6 inflammatory mediators and down-regulated nuclear factor kappa B (NF-κB) activation and TLR4/MyD88 expression [17]. In addition, *C. indicum* extract was discovered to prevent the activation of both latent infection membrane protein 1 carboxy-terminal activating region (CTAR)-1 and CTAR2-induced translocation of NF-κB by suppressing inhibitory kappa-B kinase (IκK)-α activation [23]. A similar finding showed that the flavonoid compound isolated from Chrysanthemum significantly regulated mucin secretion, production, and gene expression by acting on airway epithelial cells via the NF-κB signaling pathway [24]. NF-κB is an inducible transcription factor that promotes the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines.

Inflammation typically acts as a defense mechanism that helps maintain host health by restoring tissue balance through cellular and molecular processes. However, persistent inflammation contributes to the development of several chronic diseases. The transcription factor NF-κB serves as a mediator of inflammatory responses by inducing the expression of pro-inflammatory genes, including those encoding cytokines and chemokines. Chrysanthemum has been shown to have anti-inflammatory effects, including the ability to target genes involved in inflammation development and progression. Activation of the Janus Kinase (JAK)-signal transducer and activator of transcription (STAT)3 signaling pathway plays a crucial role in cancer development and progression as well as stimulates the expression of genes that promote invasion and metastasis. The activation of NF-κB further regulates inflammation. Oxidative stress may also initiate an inflammatory response, which generates additional free radicals that can cause more oxidative stress, creating a self-perpetuating cycle. Chrysanthemum activates the nuclear factor erythroid 2–related factor (Nrf2) signaling pathway, thereby enhancing the expression of antioxidant enzymes. The various mechanisms of Chrysanthemum in anti-inflammatory response have been demonstrated in Figure 1. It is noteworthy to mention that the correlation among the anti-inflammatory, antioxidant, anticancer, and antidiabetic properties across Chrysanthemum species highlights their potential as versatile therapeutic agents capable of holistically addressing a range of health challenges.

Antioxidant

Intracellular antioxidant enzymes, which include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are endogenous antioxidants responsible for protecting the cells from oxidative damage. Small-molecule antioxidants have long been considered compounds that can decrease oxidative stress. Free radicals generate the lipid peroxidation process in an organism where malondialdehyde (MDA) is a byproduct of polyunsaturated

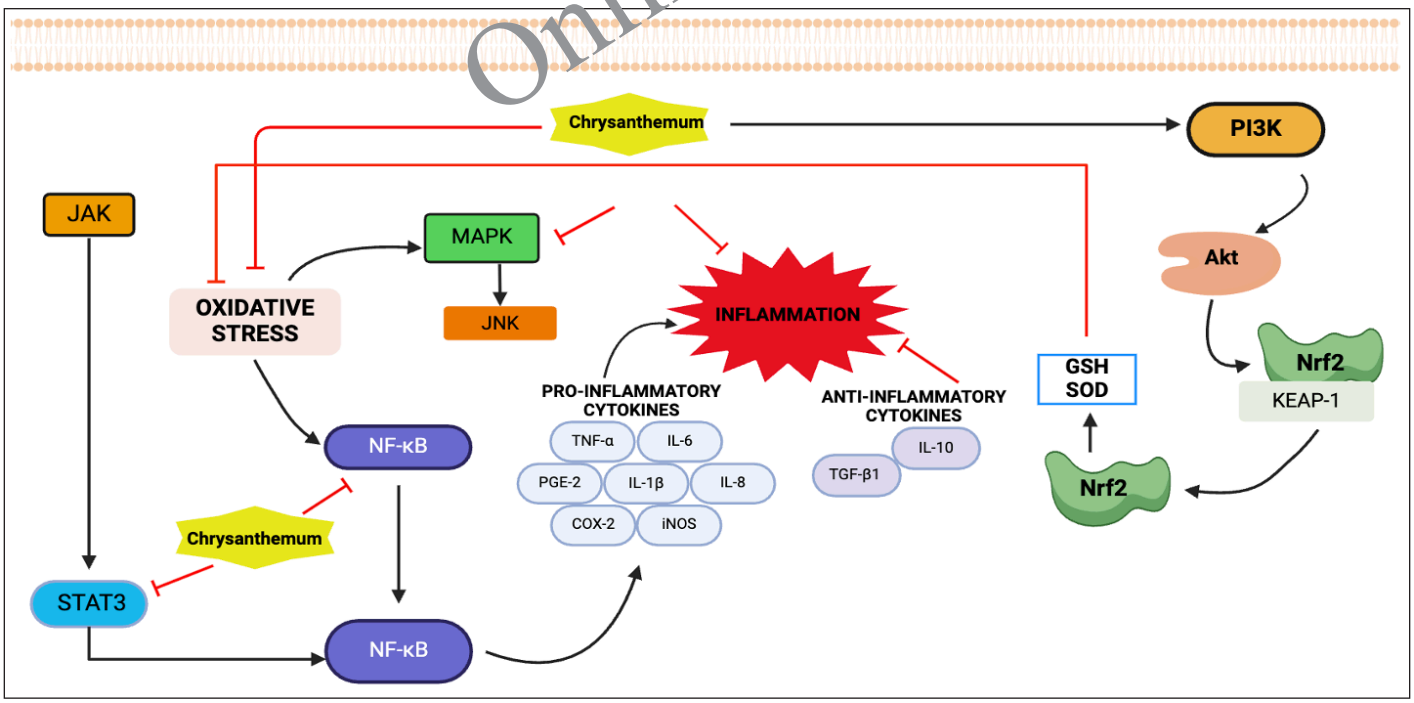

Figure 1. Molecular mechanism of anti-inflammatory of Chrysanthemum.

Abbreviation: Akt: protein kinase B, COX-2: cyclooxygenase-2, IL-6: interleukin-6, IL-8: interleukin-8, IL-10: interleukin-10, JAK: janus kinase, JNK: Jun N-terminal kinase, MAPK: mitogen-activated protein kinases, Nrf2: nuclear factor erythroid 2–related factor 2, NF-κB: nuclear factor kappa B, PI3K: phosphoinositide 3-kinase PGE-2: prostaglandin-2, STAT3: signal transducer and activator of transcription 3, TGF-β1: tumor growth factor-β1, TNF-α: tumor necrosis factor-α.

fatty acid peroxidation in cells [25]. Increased free radicals caused the overproduction of MDA and were used to evaluate oxidative stress and antioxidant status. Therefore, the ability to interact with different redox signaling pathways by altering redox enzymes' activity is the primary key to their antioxidant action.

Oxygen free radicals primarily cause damage by destroying the structure and function of the cell membrane, lipid peroxidation, deoxyribonucleic acid (DNA), mitochondria, endoplasmic reticulum, and cell death [26]. To explore the potential mechanism of *C. morifolium* as an antioxidant effect, Tian *et al*. investigated the effects of acetaminophen (APAP)-induced on liver injury in hepatocytes HL-7702 cells [27]. Treatment significantly suppresses hepatic oxidative stress by lowering ROS production and increasing the antioxidant enzymes glutathione (GSH) and SOD activity. Results also showed that *C. morifolium* intensified the nuclear translocation of Nrf2 and protein expression in the nucleus. Under normal conditions, Nrf2 is retained in the cytoplasm by binding to the negative regulator Keap1 [28]. Oxidative stress caused by a high level of ROS resulted in the dissociation of Keap1 from Nrf2, followed by translocation into the nucleus. This event initiates the expression of antioxidant genes and enzymes by binding to the antioxidant response element of the target gene promoter region [29,30]. Further investigations, in a rat model of APAP-induced liver injury, *C. morifolium* at 110, 220, and 440 mg/kg significantly reduced serum aspartate transaminase (AST) and alanine transaminase (ALT) as well as in ROS levels while upregulated SOD and GSH levels. Treatment inhibited apoptosis induced by APAP through the phosphoinositide 3-kinase/protein kinase B (PI3K–Akt) pathway and restored the ability of mitochondrial biogenesis, promoting nuclear translocation of Nrf2 [31]. Results suggest that the antioxidant capacity protects the liver from hepatotoxicity. *Chrysanthemum morifolium* was also observed to increase the total antioxidant capacity (T-AOC) activity and decrease MDA content in a dose-dependent manner of 50, 100, and 200 mg/kg [10].

The ability of antioxidants to reduce damage caused by free radicals by giving the hydrogen atoms to convert them into stable molecules is a crucial indicator of their effectiveness. Total antioxidant activity and the scavenging capacity of hydroxyl radicals and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals from Chrysanthemum were reported to be stronger than those of vitamin C as it significantly increased the SOD and T-AOC activity and decreased MDA content [32]. DPPH is the most stable free radical species that can accept electron or hydrogen radicals and is widely used to assess natural antioxidant activity. Besides, *C. indicum* has been shown to increase the activity of antioxidant enzymes including SOD, CAT, and GPX while decreasing the NF-κB activation [33]. In parallel, the protective effect of *C. indicum* extract on D-galactose-induced brain and liver damage alleviated the abnormal alterations by restoring normal antioxidant enzyme activities (SOD, GPx, and CAT) and reducing MDA accumulation [19]. Treatment also attenuated the decline of thymus and spleen indexes and reduced the elevated levels of AST and ALT liver markers. Keeping these liver indicators within the normal range significantly predicts favorable clinical outcomes, particularly for liver diseases. Distinctly decreased levels of oxidant enzymes of myeloperoxidase and MDA were also illustrated in another study, indicating the antioxidant properties of *C. indicum* [18]. Moreover, *C. indicum* was found to prevent ultraviolet (UV)-induced skin damage by lowering intracellular ROS levels and inhibiting p38 mitogen-activated protein kinases (MAPK) phosphorylation in human immortalized keratinocytes HaCat cells [34].

Anticancer

A type of programmed cell death called apoptosis is crucial for protecting the host against tumor progression. Two main pathways, which include intrinsic and extrinsic, are involved in the mechanism of cancer cells [35]. In response to intracellular stressors such as cytokine deprivation and DNA damage, the intrinsic pathway mediated by the mitochondrial activates caspase-9. Meanwhile, the death receptor-mediated extrinsic pathway activates caspase-8 when ligand-mediated trimerization of TNF family death receptors on the plasma membrane occurs. Both of these initiators caspases cleavage and activate the effector caspase-3, which deconstructs cells by cleaving several vital cellular proteins [36]. In addition, the Jun N-terminal kinase (JNK) signaling pathway is an essential regulator of cellular phenotypes in tumorigenesis. It is well-known for its ability to increase the expression of pro-apoptotic genes through transactivation of c-Jun/AP1 dependent or p53/73 protein-dependent mechanisms, thereby promoting apoptosis in the death receptor-initiated extrinsic pathway. Activated JNK translocate to the mitochondria in pathways that target mitochondrial apoptotic proteins can phosphorylate the BH3-only family to counteract the anti-apoptotic activity of B-cell leukemia/lymphoma 2 (Bcl-2) or B-cell lymphoma-extra-large [37]. Promising anticancer properties on several cancerous cell lines, including breast, lung, gastric, bone, and prostate, were discussed and summarised in Table 1.

Chrysanthemum morifolium is cytotoxic to human breast cancer lines of MCF-7 with the lowest cell viability at 312 µg ml^{-1} [38]. Target validation of Chrysanthemum phytochemicals using molecular docking demonstrated that it belongs to estrogen receptors (ESR1 and ESR2) and progesterone receptors, which are effective therapeutic targets in breast cancer. Moreover, flavonoids extracted from *C. morifolium* also inhibited cell proliferation by promoting apoptosis of human gastric cancer MKN45 in a dose (5, 10, and 20 mg/ml) and time (24 and 48 hours) dependent manner [39]. Besides, findings also demonstrated *C. morifolium* signal autophagic degradation induces apoptosis and causes pre-G1 and G0/G1 arrest in Ub-signaling HepG2 cells [40].

In addition, treatment with *C. indicum* extracts significantly sensitized multidrug-resistant human breast carcinoma cell line MCF7/ADR at nontoxic concentrations. An increase in Rh123 accumulation and a decrease in Rh123 efflux were observed, indicating a blockage of the P-glycoprotein activity [41]. P-glycoprotein is an established membrane transporter that can efflux drug molecules out of cancer cells, decreasing cancer treatment efficacy. As an adaptive response,

Table 1. Anticancer properties of *Chrysanthemum: morifolium* and *indicum* in various models and their molecular actions.

Model	Treatment	Molecular action	Reference
Human breast cancer MCF-7 cells	*C. morifolium* from National Research Center of Ornamental Plants, Mahallat, Iran (78, 156, 312, 625, 1,250, 2,000, and 5,000 µg ml^{-1})	• Cytotoxicity • Target to estrogen receptors (molecular docking analysis)	[48]
Human gastric cancer MKN45 cells	*C. morifolium* from Tongxiang Datong Industrial andTrading Co., Ltd. (0, 5, 10, and 20 mg/ml)	• Inhibited cell proliferation and induced apoptosis	[49]
Ub-signaling HepG2 cells	*C. morifolium* from Chinese medicine store (Tainan, Taiwan) (100 and 500 µM)	• Induced ubiquitin signal autophagic degradation • Induced apoptosis	[50]
Multidrug-resistant human breast carcinoma MCF7/ADR cells	*C. indicum* from Affiliation Hospital of Anhui College of Traditional Chinese Medicine (10 µg/ml)	• Increased Rh123 accumulation and decrease Rh123 efflux • Blocked P-glycoprotein activity	[51]
Fibroblast MRC-5 cells and lung carcinoma A549 cells	*C. indicum* from Guangzhou Qingping (20, 40, 60, 80, 100, 200, 400, 800, and 1000 ng/ml)	• Inhibited MMP-3/MMP-9 and promoted TIMP-1	[52]
Human alveolar basal epithelial A 549 cells	*C. indicum* from mountainous area in Chuncheon City, Republic of Korea (0.5, 1.0, and 2.0 mg/ml)	• Suppressed Akt activation	[54]
Hepatocellular carcinoma mouse H22 cells inoculated through the abdomen into male Kunming mice	*C. indicum* from Institute of New Drug Research and Development Guangzhou University of Chinese Medicine (240, 360, 480 mg/kg)	• Induced apoptosis with caspase-3/-8 activation • Upregulated p53 and activated miR-29 gene expression	[18]
TRAIL-resistant glioma cells and human glioma xenograft of male balb/c athymic (nu/nu) mice	*C. indicum* (Linarin) from Chengdu MUST Biotechnology Co. Ltd (Chengdu, China) (in vitro: 0, 2.5, 5, and 10 µM) (in vivo: 25 mg/kg)	• Induced apoptosis	[57]
D-gal-induced brain and liver injury in male Kunming mice	*C. indicum* from Institute of New Drug Research and Development, Guangzhou University of Chinese Medicin (100, 150, 300 mg/kg)	• Down-regulated Bax/Bcl-2 • Activation of caspase-3	[19]
Human osteosarcoma U-2OS cells	*C. indicum* (Chrysanthemulide A) (5, 10, 15, 20, 25, and 30 µM)	• Induced apoptosis with caspase-8 activation • Phosphorylation of JNK	[58]
Prostate cancer DU145 cells	*C. indicum* from Kyungdong market, Korea (10, 30, and 50 µg/ml)	• Cytotoxicity • Activation of caspase-3 • Suppressed JAK1/JAK2 and STAT3	[59]

Abbreviation: MMP-3/-9: matrix metalloproteinase-3/-9, TIMP-1: tissue inhibitor of metalloproteinase, Akt: protein kinase, Bcl-2: B-cell leukemia/lymphoma 2, Bax: Bcl-2-associated X protein, JNK: Jun N-terminal kinase, JAK 1/2: Janus Kinase/1/2, STAT3: signal transducer and activator of transcription 3.

cancer cells increase the expression of P-glycoprotein to avoid chemotherapy-induced cell death. Molecular analysis revealed that *C. indicum* inhibited the increment in both matrix metalloproteinase (MMP)-3 and MMP-9 while decreased tissue inhibitor of metalloproteinase 1 (TIMP-1) of MRC-5 fibroblast cells and A549 lung carcinoma [42]. MMP-induced cell apoptosis by targeting apoptotic proteins of Bax-2, Bcl-2, and cleaved caspase-3 [43]. Results suggest that the treatment suppresses Akt activation and induction of cyclin-dependent kinase inhibitor p27K in A549 human alveolar basal epithelial cells lung cancer [44]. As an apoptosis regulator, Akt activation will phosphorylate several proteins involved in cancer progression. Findings from molecular docking illustrated that the inhibition of the PI3K-Akt signaling pathway and activation of the mitochondrial-mediated apoptosis pathway supported the anti-tumor activity of the active compound in Chrysanthemum on lung cancer [45]. In addition, *C. indicum* promoted cell apoptosis by mediating the activities of caspases-3/-8, up-regulated the protein expression of p53 and miR-29b gene activation [18].

The extrinsic apoptotic pathway involves transmembrane receptor-mediated interactions between death ligands, including the first apoptosis signal ligand, TNF-related apoptosis-inducing ligand (TRAIL), and death receptors [46]. Xu *et al*. demonstrated the flavonoid compound from *C. indicum* effectively induced apoptosis against TRAIL-resistant glioma cells [47]. Apoptosis was evidenced by enhanced cleavage of caspase-8/-9/-3 and poly (ADP-ribose) polymerase (PARP) and reduced anti-apoptotic proteins, including Bcl-2. Analysis *in vivo* further confirmed that treatment significantly suppressed the xenograft growth. Besides, the protective effect of *C. indicum* in ameliorating D-gal-induced brain and liver impairments down-regulated the rise in Bax/Bcl-2 ratio and activation of cleaved caspase-3 where it was postulated to be associated with the inhibition of apoptosis [19]. Besides, Chrysanthemum also induced apoptotic cells significantly in osteosarcoma U-2OS cells through activated caspase-8-mediated caspase cascade and phosphorylation of JNK [48]. Treatment sensitized the osteosarcoma cells to the death receptor 5 ligands TRAIL-induced apoptotic cell death. Strong cytotoxic activity of *C. indicum* was exhibited by suppressing the constitutive STAT3

activation against prostate cancer cell DU145 [49]. Treatment caused cell accumulation in the sub-G1 and induced caspase-3-dependent apoptosis. Both the JAK1 and JAK2 signals that function to regulate the inflammatory response were suppressed in a dose-dependent manner. Treatment significantly decreased the ratio of TIMP1 and MMP13, contributing to the caspase-8/-9/-3 cleaved activation. The apoptotic effect was verified by its ability to cleave caspase-3/-9 and suppress the JAK2/STAT3 signaling pathway.

Antidiabetic/anti-obesity

Diabetes is a common chronic metabolic disorder characterized by abnormal glucose and lipid metabolism modulation and has become a significant public health issue. The WHO predicts that diabetes already affects more than 30 million people, and by 2025, that number is anticipated to double [50]. When a person gains weight, the cells in their body predisposed to diabetes become less sensitive to the insulin released by the pancreas. This results in insulin resistance, in which the insulin ratio exceeds the blood sugar level. Obesity is responsible for 80%–85% of the risk of developing type 2 diabetes. The Asian population uses Chrysanthemum as a traditional medicine and herbal tea for obesity-related health benefits. However, the detailed mechanisms underlying the beneficial effects of these edible flowers Chrysanthemum on diabetes, obesity, and dyslipidemia have not thoroughly been discussed.

All lipidomic biomarkers, including cholesteryl esters, lys phosphatidylcholines, phosphatidylcholines, ceramides, and sphingomyelins levels in high-fat diet (HFD) mice, were returned to normal range after supplementation with *C. morifolium* extract [51]. Findings also demonstrated that *C. morifolium* significantly reduced body weight gain and epididymal white adipose tissue (eWAT) weight by stimulating mRNA expressions for thermogenesis and energy expenditure via lipid mobilization in HFD male rats. Notably, supplements improved the balance between lipid mobilization and WAT storage by reducing adipocyte inflammation and peripheral tissue lipotoxicity [52]. Flavonoid extract from Chrysanthemum reduced the lipid profile in hyperlipidemia rats relating to improved liver function such as AST, ALT, and alkaline phosphate (ALP). Supplementation also significantly improved the lipid profile levels marked by a reduction in lipid droplets and uniformly the adipocyte morphology in the liver. Lipid-metabolizing enzymes of fatty acid, cholesterol, and triglycerides associated with lipid metabolism were found to be significantly mediated by Chrysanthemum [53]. Consistent findings by Lee *et al*. indicated that *C. morifolium* extract significantly decreased serum lipid profile and gene expression involved in adipogenesis, including peroxisome proliferator-activated receptor (PPAR)-γ, sterol regulatory element-binding transcription factor 1 (SREBP-1c), and C/EBP-α. The pro-inflammation factor of adipose tissue macrophage and M1 macrophage phenotype was reduced. The authors suggested that this activity was associated with regulating glycerol-3-phosphate dehydrogenase and NF-κB activities in epididymal adipose tissue of HFD rats.

Moreover, treatment attenuates obesity-associated inflammation by modulating the muscle AMP-activated protein and the histone/protein deacetylase pathway, where the activation limits lipolysis [54]. Free fatty acid (FFA) overflow may lead to lipotoxicity, which causes hepatic steatosis and renal dysfunction in nonadipose tissues like the liver and kidney. Treatment with *C. morifolium* significantly suppressed the FFA-induced intracellular triacylglycerol accumulation in HepG2 cells by partially inhibiting the gene expression involved in lipid metabolism of SREBP-1c protein-1c and glycerol-3-phosphate acyltransferase [12]. A natural flavonoid compound from *C. morifolium* showed a potent lipid-lowering capability in the diabetic mice model by reducing serum lipid profile levels and fasting blood glucose, indicating improvement in glucose tolerance. Results suggested flavonoids directly enhance insulin signaling activity with decreased protein tyrosine phosphatase (PTP)-1B protein levels [55]. Moreover, flavonoid treatment induced insulin secretion in a high glucose-treated insulinoma cell line insulinoma (INS)-1 model. The PTP-1B signaling pathway is a potential therapeutic target for type 2 diabetes. The inhibition improved glucose homeostasis and insulin signaling without causing lipid buildup in the liver. In the type 2 diabetic mice model, *C. morifolium* decreased adipocyte size and improved insulin resistance by significantly reducing blood glucose levels.

Supplementation increased the mRNA levels of adiponectin by upregulating PPAR-γ while decreasing pro-inflammatory adipocytokines [56]. Improvements in insulin resistance and down-regulation of blood glucose levels as well as liver lipid content indicate its potential as antidiabetic in type 2 diabetic mice models. Similarly, an in vitro study showed that *C. morifolium* increased adipocyte differentiation, adiponectin secretion, and glucose uptake in murine preadipocyte 3T3-L1 cells. Treatment elevated the mRNA levels of PPAR, C/EBP-α, and glucose transporter type (GLUT) 4 expression [57]. The author postulated that the existing extracts contained polyphenols, and corresponding glycosides might be associated with higher PPAR-γ expression. Nevertheless, additional research is required to confirm the mechanism that explains the rising PPAR γ expression. Further study has identified the anti-diabetic components in the isolated compounds from *C. morifolium* functioned to increase intracellular lipid accumulation and adiponectin secretion while decreasing 3T3-L1 cell diameter during adipocyte differentiation suggested regulating PI3K/Akt Pathway and PPARγ [58].

Nepali *et al*. examined the effects of *C. indicum* in high-fat-diet (HFD)-induced obese mice on the basic panels of serum lipid profile. Findings showed that supplementation significantly decreased total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLc) while increasing high-density lipoprotein cholesterol (HDLc) levels [59]. LDL particles, which vary in size and density, carry most cholesterol in circulation. On the other hand, HDL particles are high in cholesterol and phospholipids, which aid in reverse cholesterol transport from peripheral tissues to the liver. Significantly inhibited serum leptin and increased adiponectin levels were also observed in HFD mice. Effects on adipogenesis were indicated by upregulated the AMP-activated protein kinase (AMPK)

phosphorylation and suppressed transcriptional factors of PPAR-γ and CCAAT/enhancer-binding protein (C/EBP)-α.

Chrysanthemum indicum was highly efficient in converting glycosides to aglycones when combined with enzymes (viscozyme and tannase), potentially suppressing adipogenesis and lipid accumulation. Reduction in body weight, lipid accumulation, serum lipid profile (TC, TG, and LDLc), and leptin levels were observed in HFD male mice by effectively downregulating the adipogenesis-related transcription factors of PPAR-γ and C/EBP-α [60]. Similarly, treatment with Chrysanthemum was found to decrease leptin and increase adiponectin levels by significantly up-regulated the protein expression level of PPAR-α while down-regulated the PPAR-γ and C/EBP-α [61]. Both PPAR and C/EBP factors play a crucial element in regulating adipogenesis. The ligand-activated transcription factor family PPAR is an important target for obesity and metabolic syndrome because it promotes the ligand-dependent transcription of target genes that regulate energy generation and lipid metabolism [62]. In obesity, a high level of leptin will cause leptin resistance, leading to high food intake and decreased energy expenditure. In contrast to leptin, low adiponectin levels lead to gluconeogenesis, hyperlipidemia, and increased glycemia resulting in metabolic syndrome.

Inhibiting the activities of α-glucosidase and pancreatic α-amylase will help manage postprandial hyperglycemia and aggressively delay the breakdown of carbohydrates into absorbable monosaccharides. A study demonstrated that the combination of *C. indicum* extract produced synergistic inhibition against pancreatic α-amylase [63]. This enzyme hydrolyses alpha bonds of large, α-linked polysaccharides, such as starch and glycogen, yielding shorter chains. The α-amylase inhibition can control the breakdown of dietary starch into smaller oligomers, thereby delaying glucose absorption. A bioactive compound from Chrysanthemum illustrated an inhibitory effect of α-amylase and α-glucosidase in a dose-dependent manner, as the α-glucosidase inhibition is a key to carbohydrate hydrolyzing [64]. Overall, the data suggested that Chrysanthemum administration was beneficial for controlling hyperglycemia and hyperlipidemia as well as possibly preventing diabetic complications by suppressing the transcriptional factors required for adipogenesis that attributed to the anti-adipogenicity properties are summarised in Table 2.

Antimicrobial

Antimicrobial property is not only limited to prevention against bacterial activity, but it comprises all scopes of protection such as antiviral, antifungal, antibiotic, and antibacterial. It prevents the formation of bacterial colonies by stifling or inhibiting the growth of bacteria from spreading within or onto an organism. The main concern on antimicrobial properties globally is the increase of lower effectiveness of antibiotics and microbial resistance to medications [65]. Lack of preventive measures for infection and overuse or misuse of antimicrobial products contribute to the complication. The rising of natural resources awareness in medicines has brought numerous studies on antimicrobial properties. Most anti-bacterial studies were evaluated based on the minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) values, and zone of inhibition. The MIC, MBC, and bacteria effects on the inhibition area may vary according to the type of bacteria, the source used, and the dosage applied to the tested microorganisms. Using different bacteria types, the study by Hodaei *et al*. revealed that *C. morifolium* has significant antibacterial properties on *Salmonella enterica* and *Bacillus cereus* ranging from 5–10 mg/ml^{-1} and for *Staphylococcus aureus* and *Escherichia coli* ranging from 10–20 mg/ml^{-1} [66]. Higher MIC values mean lower susceptibility to *C. morifolium* extract [67]. The MIC values represent the ability of an antibacterial agent to inhibit microorganisms' growth at the lowest concentration of drug or chemical. Similar outcomes were obtained from another study whereby Chrysanthemum buds from morifolium extract exerted inhibitory activity on *Cronobacter sakazakii* bacteria (a food-borne pathogen that can be hazardous to infants or newborns) at 10 mg/ml MIC values [68]. On the other hand, a study by Yeasmin *et al*. demonstrated that extract from flower parts of *C. morifolium* gave out MIC values ranging from 150–250 mg/ml against ten pathogenic bacteria comprising Staphylococcus aureus, Bacillus cereus, *Streptococcus-β-haemolytica, Bacillus subtilis, Sarcina lutea, Klebsiella sp, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella typhi*, and *Shigella dysenteriae* [69]. They also evaluated the impact of extraction techniques on antibacterial activity, where their data revealed that *C. morifolium* had a 24.40 mm larger inhibitory zone.

In addition, *C. indicum* was effective against food-borne pathogens (gram-positive and gram-negative bacteria) of *S. typhi, Clostridium perfringens* and *Listeria monocytogenes* [70]. The high content of polyphenolic compounds such as flavonoids can be extracted successfully, indicating its involvement as essential in inducing antibacterial activity. Reactions between the plant-derived compound with enzymes and protein of microbial cell membrane induce antibacterial activity or inhibition [71]. Somehow, variation in antibacterial activity can be due to the various phytochemical compounds in an extract [66]. In the antiviral aspect, a study by Ming *et al*. demonstrated that phosphorylated *C. indicum* polysaccharide possesses a better antiviral activity against duck hepatitis A virus [72]. Studies have also revealed that *C. indicum* extracts have larvicidal and pupicidal effects on the malaria vector of *Anopheles stephensi* mosquito marked by killing the plasmodium [73].

Other properties

The effect of two Chrysanthemum species on other diseases was limited and poorly documented. In bone metabolism, findings showed that *C. morifolium* extracts significantly inhibit osteoclast differentiation without cytotoxic effects [74]. Osteoclasts are the cells responsible for the degradation of bone to initiate normal bone remodelling and mediate bone loss. The resorption of bone by osteoclasts and the formation of bone by osteoblasts are essential for bone homeostasis. Imbalances in this tightly coupled process can result in diseases like osteoporosis. Ovariectomized rat was a well-known animal model to induce postmenopausal osteoporosis, in which findings indicated that supplementation could be an alternative to manage this disease. In addition,

Table 2. Antidiabetic properties of *Chrysanthemum: morifolium* and *indicum*.

Model	Treatment	Findings	Reference
HFD-induced dyslipidemia in male C57BL/6J mice	*C. morifolium* from Haihang Industry, Jinan, China (1.5% w/w)	• ↓ Lipidomic biomarkers: cholesteryl esters, lysophosphatidylcholines, phosphatidylcholines, ceramides, and sphingomyelins	[61]
HFD-induced obese in male C57BL/6 mice	*C. morifolium* from Haihang Industry Co., Ltd. (Jinan, China) (1.5%, w/w)	• Decreased lipid profile and eWAT • ↓ Adipocytes inflammation and peripheral tissue lipotoxicity	[62]
HFD-induced hyperlipidemia male Sprague-Dawley rats	*C. morifolium* from the Nanjing Zelang Pharmaceutical Company (100 mg/kg)	• Decreased lipid profile: ↓ TC, TG, LDL • ↓ Lipid droplets and adipocytes • ↓Lipid peroxidation • Regulated lipid synthesis enzymes: fatty acid (↓FAS, ↑FAβO), cholesterol (↓HMG-CoAR, ↑CYP7A1), and triglycerides (↓DGAT, ↑HL)	[63]
HFD diet-induced obese in male Sprague–Dawley rat	*C. morifolium* from Amway Korea (Seoul, Korea) and Amway China R&D (Shanghai, China) (0.2% and 0.4%)	• Decreased lipid profile: ↓ TC, TG, LDL • Downregulated PPAR-γ, SREBP-1c and C/EBP-α transcription factors	[64]
HepG2 cells	*C. morifolium* from Shiding, New Taipei, and Tongluo, Miaoli, Taiwan (25, 100 μg/ml)	• Suppressed FFA-induced intracellular triacylglycerol • Decreased lipid accumulation and pro-inflammatory markers	[12]
Diabetic mice model High glucose-treated insulinoma cell line INS-1 model	*C. morifolium* from Tianfu Tea Co. Ltd (Zhejiang China) (in vivo:50 and 100 mg/kg) (*in vitro*: 0.1, 1, 10, and 100 μM)	• Decreased lipid profile: ↓ TC, TG • ↓ Fasting blood glucose • ↑ Insulin signaling activity: ↓ PTP-1B protein	[65]
Type 2 diabetic mice model	*C. morifolium* from Yamagata, Japan (Fed 1% and 5%)	• ↓ Blood glucose level • ↑ Adiponectin	[66]
Mouse 3T3-L1 preadipocytes	*C. morifolium* from Yamagata, Japan (0.1, 0.3, and 1 mg/ml)	• Enhanced adipocyte differentiation, adiponectin secretion, and glucose uptake through C/EBPδ-induced PPARγ expression	[67]
Mouse 3T3-L1 preadipocytes	*C. morifolium* from Yamagata Prefecture, Japan (3, 10, 30, and 100 μM)	• ↑ Adiponectin • ↓ Adipocytes diameter	[68]
HFD-induced obese in male C57BL/6 mice	*C. indicum* from BTC corporation (Sangnok-gu, Ansan 15,588, Korea) (100 and 200 mg/kg)	• ↓ Fat volume (lipid accumulation) • Decreased lipid profile: ↓ TC, TG, LDL • ↓Leptin level • Downregulated PPAR-γ and C/EBP-α transcription factors	[70]
HFD-induced obese in male C57BL/6 mice	*C. indicum* from Gungangbogam (Jechon, Korea) (8, 40 200 mg/kg)	• ↓ eWAT • ↓ Leptin and ↑ adiponectin levels • Upregulated PPAR-α and downregulated PPAR-γ and C/EBP-α transcription factors	[71]
Rat intestinal	*C. indicum* from Bangkok, Thailand (1 mg/l)	• Inhibited pancreatic α-amylase	[73]

Abbreviation: AMPK: AMP-activated protein kinase, C/EBP-α/β/γ: CCAAT/enhancer binding protein-α/-β/-γ, CYP7A1: cholesterol 7-alpha-monooxygenase, DGAT: diglyceride acyltransferase, eWAT: epididymal white adipose tissue, FFA: free fatty acid, FAS: fatty acid synthase, FAβO: fatty acid beta-oxidation, TC: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein, HDL: high-density lipoprotein, PPAR-γ/-α: peroxisome proliferator-activated receptor-γ/-α, HMG-CoAR: 3-hydroxy-3-methylglutaryl coenzyme A reductase, HL: hepatic lipase, PTP-1B: protein tyrosine phosphatase 1B, SREBP-1c: sterol regulatory element-binding transcription factor 1.

C. morifolium supplementation was found to attenuate sarcopenia by promoting the phosphorylation of PI3K-Akt and mammalian target of rapamycin pathways, which stimulate the synthesis of muscle proteins [75]. Findings revealed that *C. morifolium* treatment enhanced grip strength, muscle mass and volume, and cross-sectional area of myofibers in middle-aged C57BL/6J mice, suggesting that it can delay the onset of sarcopenia by enhancing the recovery and functionality of muscle mass.

Li *et al*. discovered that an active compound from *C. indicum* increased ALP and extracellular matrix mineralization in MC3T3-E1 cells in a dose-dependent manner, as evidenced by increased osteoblast proliferation and differentiation. The finding also observed the upregulation of osteogenesis-related gene expression, including ALP, runt-related transcription factor-2, osteocalcin, bone sialoprotein and type I collagen in the treatment group, which later preserved the trabecular bone microarchitecture of ovariectomized mice [76]. Furthermore, *C. indicum* demonstrated antiosteoporosis properties in receptor activator of nuclear factor-B ligand (RANKL)-induced osteoclastic RAW 264.7 cells by inhibiting

excessive bone resorption accompanied by a decrease in tartrate-resistant acid phosphatase activity [77].

A major contributing factor to gout, known as hyperuricemia is an abnormally excessive accumulation of uric acid brought on by an imbalance between uric acid production and excretion. Treatment with *C. indicum* extract significantly increases the expression levels of the organic anion transporter 1 (OAT) and OAT 3 proteins both *in vitro* and *in vivo* while suppressing the activity of xanthine oxidase and mRNA expression of xanthine dehydrogenase [78]. A study by Lee *et al*. also indicated a reduction of serum uric acid levels in normal rats and rats with uricase inhibitor potassium oxonate-induced hyperuricemia while increasing renal uric acid excretion after treatment with *C. indicum* [79]. In addition, treatment with *C. indicum* effectively suppressed UV-induced increase in skin thickness and wrinkle grading in a dose-dependent manner, correlated with inhibition of collagen fiber content loss and epidermal thickening on mouse skin [80]. Solar UV radiation is known to cause skin damage primarily through superfluous ROS and chronic low-grade inflammation, which eventually up-regulate the expression of MMPs. Therefore, treatment inhibited the production of inflammatory cytokines, alleviated abnormal changes in anti-oxidative indicators, and down-regulated the levels of MMP-1 and MMP-3, indicating *C. indicum* role as a novel photoprotective agent. *Chrysanthemum indicum* also exhibited its function in maintaining healthy skin by increasing the expression of pro-collagen 12, collagen 12, and fibronectin. All these findings may provide valuable data for developing edible flowers as functional products.

TOXICITY AND SAFETY OF CHRYSANTHEMUM

Chrysanthemum toxicity studies have been investigated to characterize and identify potential adverse effects with various doses administrated. In a single-dose administration of *C. morifolium* at 15 g/kg body weight dose, no death was reported in rats after 14 days of observation. Similarly, no acute toxicity and side effects were observed in rats after orally being treated with Chrysanthemum at 0, 1, and 2 ml/kg body weight after 14 days of observation [81]. Oral administration of *C. morifolium* for long-term toxicity at doses of 320, 640, and 1280 mg/kg body weight/d for 26 weeks, followed by a 4-week recovery period, was observed to be safe [76]. A study by Hwang *et al*. reported no mortality and clinical signs of toxicity after oral administration of *C. indicum* at 2,000 mg/kg body weight/d for 15 days in mice [82]. Another study showed that high *C. indicum* at 1,024, 1,280, 1,600, and 2,000 mg/kg were reported safe, with no toxic alteration found in mice [83]. To date, no abnormalities were observed in another randomized, double-blind, placebo-controlled trial after 12-week ingestion of Chrysanthemum extract at 100 mg/d doses [84]. Interestingly, the administration of Chrysanthemum extracts at a higher dose of 400 mg/d (200 mg/ml, twice/day) exhibited antioxidant properties by demonstrating its neuroprotective effect on ischemic stroke patients [85]. Several studies have reported no adverse effects related to Chrysanthemum, which indicates its safety. However, there is still limited scientific information to determine an appropriate range of doses for Chrysanthemum, especially in a clinical study. The appropriate dose of Chrysanthemum intake still depends on several factors, including age, health, and other conditions. Nevertheless, further clinical safety studies on Chrysanthemum should still be carried out to validate the findings.

CHRYSANTHEMUM NANOPARTICLES AS GREEN NANOMEDICINE AND OTHER APPLICATION

In the modern era, there has been a growing interest in sustainable and eco-friendly practices including in the field of nanotechnology, leading to the emergence of green nanomaterials. Due to their peculiar physiochemical properties, such as a high ratio of surface area to mass, electric optical, catalytic, and therapeutic properties, nanomaterials are extensively used and studied [86,87]. Green nanomaterials are aimed to be derived from renewable sources, such as plant compounds, and represent a promising strategy for addressing the environmental and health concerns associated with conventional synthetic methods, which usually require high pressure and temperature for operations, expensive equipment and the usage of harsh chemicals and reagents that are noneco-friendly [88]. Among the wide variety of green nanomaterials, those synthesized from plant extracts have garnered the most interest due to their inherent biocompatibility, abundance, and low production costs. Therefore, a burgeoning research field focusing on Chrysanthemum species for nanomaterials synthesis as a candidate has been implied. Utilizing the natural potential of nanoparticles derived from Chrysanthemums for their diverse effects and potential applications will pave the way for more sustainable and eco-friendly nanotechnology.

In previous studies, silver nanoparticles (AgNPs) synthesized from *C. indicum* extract revealed antimicrobial activity on *K. pneumonia, E. coli*, and *P. aeruginosa,* as confirmed by the Kirby–Bauer disc diffusion method. The study emphasized the spherical and hexagonal with the range size of 37.71–71.99 nm AgNP created from the Chrysanthemum aqueous extract that is rich in tannins, saponins, flavonoids, terpenoids, alkaloids, steroids, and glycosides as their active compounds [89]. Moreover, biocompatibility tests conducted on mouse embryo fibroblast cells indicate the safety of nanoparticles. This observation aligns with the most recent observation on *C. indicum* nanoparticles, highlighting well-dispersed and capping silver nanoparticles with a size range between 71 and 180 nm [86]. The *C. indicum* extract served as both a reductant and a stabilizing agent for the synthesis of spherical nanoparticles. In addition, further investigation was continued on AgNPs synthesised by Chrysanthemum to optimise various parameters, including extraction concentration, pH, time, and reaction temperature. The investigation yielded 1.98 ± 0.57 nm particle size, demonstrating excellent bacterial resistivity on *E. coli* and *Staphylococcus aureus*, thereby aiding in bacterial reduction and azo-contaminated wastewater treatment [90].

The outcome proportionally aligns with another *C. morifolium* study showing potent bactericidal activity against the same bacteria prioritized in wastewater treatment [91]. The study has yielded 20–50 nm nanoparticle size observed under transmission electron microscopy. This is in agreement with the utilization of Chrysanthemum spp. in the synthesis of $ZnFe_2O_4$@

ZnO nanocomposite for Congo red dye degradation with a remarkable rate of efficiency, 94.85% discharged in wastewater. The nanocomposite displayed an increased surface area between 7.41–42.66 m^2 g^{-1} and a decreased band gap energy from 1.98 to 1.92 eV, enhancing its efficiency in dye degradation. The dye is often used in printing, textile, color paper, and leather products, which is unfortunately detrimental to the environment and carcinogenic [92]. An additional investigation explored the antioxidant and antibacterial characteristics of AgNPs derived from six distinct varieties of *C. morifolium*. The study indicated that spherical AgNPs with a size of approximately 40 ± 1.2 nm were successfully generated from the five varieties under examination. Furthermore, the nanoparticles were classified as semiconductors, as observed from scanning electron microscopy images. Notably, all varieties exhibited potent antioxidant and antibacterial activity against *E. coli* and *Staphylococcus aureus* bacteria in the study [93]. Furthermore, the most recent discovery concluded that Chrysanthemum spp. extract AgNPs have the potential to be utilized in the semiconductor sector as they allow for size modification and band gap that can be used widely in biomedical instruments and applications [94].

The results of these studies underscore the significance of Chrysanthemum-based nanomaterials as eco-friendly and versatile agents with diverse applications in medicine, environmental protection, and industrial wastewater treatment. Continued research and optimization of these nanoparticles hold the potential for addressing pressing global challenges related to antimicrobial resistance and environmental pollution while promoting sustainable and green nanotechnology practices.

CONCLUSION

Natural products received an overwhelming demand in conjunction with their safety and low toxicity effect, compared to modern drugs. This present review provides an up-to-date mechanism study of anti-inflammatory, antioxidant, anticancer, antidiabetic/anti-obesity, and antimicrobial in two common Chrysanthemum species: *morifolium* and *indicum*, both *in vivo* and *in vitro* studies. The redox-regulated transcription factor Nrf2 plays a crucial role in protecting against oxidative damage by inducing the expression of cytoprotective and antioxidant genes. Chrysanthemum also possesses intriguing anti-inflammatory properties by reducing pro-inflammatory factors and genes. Findings identified that *C. indicum* study illustrated more as an anticancer property. Chrysanthemum-mediated apoptosis effects are closely related to the activation of caspase cleavage. These molecular properties depend on one another in maintaining the hemostasis process by activating several signaling pathways involved, including JNK, while suppressing the proteins and transcription factors that increase tumor progression. Meanwhile, findings on *Chrysanthemum morifolim* extracts focus on the antidiabetic/anti-obesity properties. Treatment with Chrysanthemum extracts can regulate lipid metabolism to curb obesity and diabetes, illustrated by a decrement in lipid profiles such as TC, TG, and LDL. Somehow, the clinical trials of these properties must be further validated and properly documented. Two species of Chrysanthemum flowers were similar in origin but differed slightly in their medicinal properties, which can aid in developing a research strategy plan to bridge Chinese medicine with modern precision medicine. The present review summarizes the promising therapeutics properties in the Chrysanthemum genus and will serve as a foundation for future studies on plant-based medicines.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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How to cite this article:
Mohamad NV, Zahari CNMC. Biological activities of Chrysanthemum morifolium and Chrysanthemum indicum: Molecular prospective. J Appl Pharm Sci. 2024. http://doi.org/10.7324/JAPS.2024.171645