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Review

Medicinal Importance, Pharmacological Activity, and Analytical Aspects of Marein in Medicine: An Active Flavonoid With Diverse Biological Potential

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Abstract

Coreopsis tinctoria is planted worldwide including China, Portugal and India. The capitula of *Coreopsis tinctoria* are used as a functional tea to prevent numerous human health complications, including cardiovascular diseases and diabetes. Marein also called okanin-4'-O-β-D-glucopyranoside is an important phytochemical of chalcone subgroup of polyphenols, found to be present in the flavonoid fraction of *Coreopsis tinctoria*. In the present paper we have collected all the scientific information of marein and presented in this review article in order to know the therapeutic value of marein in medicine. Scientific information of marein for their biological activities has been searched in Google, Google Scholar, PubMed, Scopus, and Science Direct and collected scientific information of marein were presented here in this review article. All the collected scientific information of marein has been analyzed in the present review paper in order to know the health beneficial aspects of marein. Present paper scientific data described the biological importance and therapeutic potential of marein for their effectiveness in SARS-CoV-2, cancer, hyperglycemia, diabetic encephalopathy, diabetic nephropathy, osteoclastogenesis, pancreatitis and renal fibrosis. Further present paper also described their intestinal absorption, antioxidant, cytoprotective potential with their effect on epidermal growth factor. However the analytical techniques of marein for its separation, isolation and identification of in various samples were also described in the present paper. Present work will be beneficial for all the researchers to know the biological importance and therapeutic potential of marein.

Keywords: Antioxidant, cancer, cytoprotective potential, diabetic encephalopathy, diabetic nephropathy, hyperglycemia, marein, osteoclastogenesis, pancreatitis, renal fibrosis, SARS-CoV-2.

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Medicinal plants consist of different types of herbs and their by-products. Herbal medicines and the phytochemicals derived from them are used in medicine to develop new types of medicines.[1–3] Natural plant products are used as medicinal products in traditional and modern medicine. Phytochemicals are natural biologically active compounds found in plants. Traditional medicinal herbs are gaining importance and popularity in the health sectors due to their medicinal properties and reduced side effects. More than 80-85% of the world's population relies on medicinal plants to meet their primary health care needs.[2,4–6] Herbal medicine is an integral part of the health care

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system in many countries, including China, India, South Korea, and Japan.[7] In most parts of the world, more than 80% of people still rely on medicinal plants to meet their primary medical needs.[8] Herbal products derived from plants and developed medicinal molecules have been used in medicine from ancient times to the modern therapeutic era as herbal medicines, nutritional supplements, perfumes, beverages, and cosmetics.[9] In our daily life, we use various types of plant products as food and medicine. Natural products derived from plants have many biological applications in modern medical systems.[10,11] Phytochemicals are an important class of natural chemicals found in various parts of vegetables, herbs, fruits, and seeds and used by humans in the form of medicines and dietary supplements.[12,13] Plant secondary metabolites also perform a variety of functions, including plant growth and development processes, innate immunity, defense signaling, and responses to environmental stress.[14] Plants constitute the most abundant source of medicines in developed and developing countries, and natural products derived from plants have long demonstrated more pronounced biological and therapeutic potential than synthetic products.[15] More than 50 percent of the medicines approved by the Food and Drug Administration (FDA) and available on the market are made from these types of natural products and their derived secondary metabolites.[16]

Coreopsis tinctoria Nutt., a member of the Chrysanthemum family, usually grows in the Karakoram Mountain in China. *Coreopsis tinctoria* buds has been used as a folk medicine for the treatment of diabetes, hypertension and hyperlipidemia. *Coreopsis tinctoria* buds were rich in polyphenol and flavonoid compounds, especially marein.[17] *Coreopsis tinctoria* Nutt. is consumed as flower tea with many health benefits, including anti-oxidant, and anti-inflammatory activity. Chemical compounds, including flavonoids, polyacetylenes, polysaccharides, phenylpropanoids, and volatile oil have been isolated from *Coreopsis tinctoria*.[18] *Coreopsis tinctoria* is native to North America but it has spread worldwide. In Portugal, two cups per day of an infusion of *Coreopsis tinctoria* flowers, known as Estrelas-do-Egipto, is traditionally used to reduce hyperglycaemia in diabetic patients.[19] Currently, at least 20 flavonoids have been found to be present in *Coreopsis tinctoria*, and marein was demonstrated to be the most abundant flavonoid.[20] *Coreopsis tinctoria* has been traditionally used for the treatment of several diseases including diabetes mellitus (DM), internal pain, and diarrhea. Marein (okanin-4'-O-β-D-glucopyranoside), belonging to the chalcone subgroup of polyphenols, is a major active flavonoid ingredient extracted from *Coreopsis tinctoria*. Marein possesses several beneficial activities including anti-oxidative, anti-inflammatory, anti-hypertensive, anti-hyperlipidemic, and anti-diabetic effects.[21] Marein, a dihydrochalcone with a structure similar to phloridzin is one of the effective phytocomponents of *Coreopsis tinctoria* Nutt. Marein improved insulin resistance in high glucose treated HepG2 cells. Marein also countered methylglyoxal-induced apoptosis in PC12 cells by activating adenosine 5'-monophosphate-activated protein kinase (AMPK). Biological effect of marein in countering diabetic nephropathy (DN) in db/db mice and high glucose-induced human tubular epithelial cells (HK-2) has been investigated in the scientific fields.[22] Marein is the main active component of flavonoids in *Coreopsis tinctoria*. Marein has effects on lowering blood sugar, regulating blood lipids, and antihypertension. Marein can resist oxidation, reduce triacylglycerol content, and have a certain protective effect on pancreatic islet cells MIN6. Marein also improves glucose metabolism disorder induced by high glucose in HepG2 cells, which could significantly prevent insulin resistance induced by high glucose. Marein can improve the abnormal glucose and lipid metabolism of hypertrophic H9c2 cells by reducing the expression of HIF-1α. It also prevents diabetic nephropathy by inhibiting the expression of SGLT2 in the kidney.[23] Marein is a major bioactive compound of *Coreopsis tinctoria* which shows activities that are beneficial in bone diseases. Marein could inhibit the generation of reactive oxygen species (ROS) and the activation of the nuclear factor kappa B (NF-κB) pathway *in vitro*. Biological effects of marein on osteoclastogenesis in RAW264.7 cells based on the NF-κB signaling pathway has been investigated.[24] Marein can improve high glucose-induced insulin resistance by mediating glucose metabolism, suggesting that marein may affect energy metabolism.[25]

Pharmacological Activities of Marein

SARS-CoV-2

Potent allosteric inhibitors of the SARS-CoV-2 main protease (Mpro) were identified and predicted through computational study. More than 100 distinct flavonoids were docked with the allosteric site of Mpro via molecular docking and simulations. Docking experiments revealed four top hit compounds, including marein that bound strongly to the Mpro predicted allosteric site. Absorption, distribution, metabolism, excretion and toxicity (ADMET) and Lipinski drug likenesses were calculated to indicate the therapeutic value of the top four hits. Further, they were non-toxic and exhibited high human intestinal absorption concentrations. These novel allosteric site inhibitors provide a higher chance of drugging SARS-CoV2 Mpro due to the rapid mutation rate of the viral enzyme's active sites. This findings provide a new avenue for developing novel allosteric inhibitors of SARS-CoV-2 Mpro.[26]

Cancer

The development of drug delivery vehicles comprised of polymeric Nanoparticles (NPs) that are surface modified with Affibody ligands that bind to the extracellular domain of the trans-membrane human epidermal growth factor receptor 2 (HER-2) for targeted delivery to cells which over express the HER-2 antigen has been investigated. Nanoparticles lacking the anti-HER-2 Affibody did not show significant uptake by these cells. Using paclitaxel encapsulated NP-Affibody (1 wt% drug loading), we demonstrated increased cytotoxicity of these bioconjugates in SK-BR-3 and SKOV-3 cell lines. These targeted, drug encapsulated NP-Affibody bioconjugates may be efficacious in treating HER-2 expressing carcinoma.[27] The *in vitro* histone deacetylase enzymes (HDACs) inhibitory activity of twenty-one natural chalcones has been investigated. Only four chalcones, including marein showed HDAC inhibitory activity with IC50 values of 60-190 μM. Molecular modeling and docking studies were performed to shed light into dual activity and to draw structure-activity relationships among chalcones that provides evidence for HDACs as potential drug targets for natural chalcones which further demonstrates that chalcones can serve as lead compounds in the development of dual inhibitors for the treatment of inflammation and cancer.[28]

Hypoglycemic Agent

Biological effects of marein on high glucose (HG)-induced injury and extracellular matrix (ECM) degradation in human nucleus pulposus cells (NPCs)(HNPCs) have been investigated. Marein effectively alleviated HG-induced viability reduction, apoptosis and ECM degradation in human NPCs (HNPCs). Marein inhibited HG-induced ROS generation and NF-κB activation in HNPCs. Marein protects HNPCs against HG-induced injury and ECM degradation by inhibiting the ROS/NF-κB pathway.[21] Biological effect of marein on improving insulin resistance in HepG2 cells has been investigated. The protective effects of marein in high glucose-induced human liver carcinoma cell HepG2 have been investigated. Marein significantly stimulated the phosphorylation of AMP-activated protein kinase (AMPK) and the Akt substrate of 160kDa (AS160) and enhanced the translocation of glucose transporter 1 (GLUT1) to the plasma membrane. Additionally, marein-stimulated glucose uptake was blocked in the presence of STO-609, however, marein-stimulated AMPK phosphorylation was not blocked by LKB1 siRNA in HepG2 cells. Marein also inhibited the phosphorylation of insulin receptor substrate (IRS-1) at Ser 612, but inhibited GSK-3β phosphorylation and increased glycogen synthesis. Marein improved insulin resistance induced by high glucose in HepG2 cells through CaMKK/AMPK/GLUT1 to promote glucose uptake, through IRS/Akt/GSK-3β to increase glycogen synthesis, and through Akt/FoxO1 to decrease gluconeogenesis. Marein could be a promising leading compound for the development of hypoglycemic agent.[19] Biological effect of marein in hypertrophic H9c2 cells has been investigated. Treating angiotensin II/hypoxia-stimulated H9c2 cells with marein led to decreasing cell surface area, intracellular total protein, atrial natriuretic peptide, and free fatty acids levels, but increasing glucose level. Marein treatment decreased hypoxia inducible factor-1α (HIF-1α), peroxisome proliferator activated receptor γ (PPARγ), medium chain acyl-coenzyme A dehydrogenase, glucose transporter-4, and glycerol-3-phosphate acyltransferase protein expressions, and increased PPARα, fatty acid transport protein-1, carnitine palmitoyltransferase-1, and pyruvate dehydrogenase kinase-4 protein expressions. Marein could ameliorate abnormal glucolipid metabolism in hypertrophic H9c2 cells, and the effects could be attributable to reduction of HIF-1α expression and subsequent regulation PPARα/γ-mediated lipogenic gene expressions.[25]

Diabetic Encephalopathy

Biological effect of marein to prevent PC12 cell damage induced by MG has been investigated using cultured PC12 cells in the presence of methylglyoxal (MG). Marein attenuated MG-induced changes in the mitochondrial membrane potential (ΔΨm), mitochondrial permeability transition pores (mPTPs), intracellular Ca2+ levels, the production of reactive oxygen species (ROS), glutathione (GSH)/glutathione disulfide (GSSG) and adenosine triphosphate (ATP), and the increase in the percentage of apoptotic cells. Marein also increased glyoxalase I (Glo1) activity, phospho-AMPKα (Thr172) and Bcl-2 expression and diminished the activation of Bax, caspase-3 and inhibitor of caspase-activated deoxyribonuclease. Importantly, pretreatment of cells with marein diminished the compound C-induced inactivation of p-AMPK. Molecular docking simulation showed that marein interacted with the γ subunit of AMPK. The neuroprotective effect of marein is due to a reduction of damage to mitochondria function and activation of the AMPK signal pathway which indicate that marein could be a potent compound for preventing and counteracting diabetic encephalopathy.[29]

Diabetic Nephropathy

Biological effects of marein in diabetic db/db mice with DN, and in high glucose-treated HK-2 cells have been investigated. *In vivo*, treating diabetic db/db mice with marein for 12 consecutive weeks restored diabetes-induced hyperglycemia and dyslipidemia, and ameliorated renal function deterioration, glomerulosclerosis, and renal ectopic lipid deposition. Marein exerted renoprotective effects by directly inhibiting renal tubule sodium glucose transporter 2 (SGLT2) expression, and then activating the AMP-activated protein kinase (AMPK)/acetyl CoA carboxylase (ACC)/per-

oxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) pathway in db/db mice. Marein ameliorated fibrosis and inflammation by suppressing the pro-inflammatory factors interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1), and expression of the extracellular matrix proteins, fibronectin (FN) and collagen 1 (COL1) in diabetic mice. *In vitro*, Marein was found to be absorbed across the membrane at a medium level. Furthermore, Marein treatment decreased SGLT2 expression in SGLT2-overexpressing HK-2 cells. In addition, molecular docking and dynamics analysis revealed that SGLT2 was a direct target of Marein. Marein ameliorates DN by inhibiting renal SGLT2 and activating p-AMPK, suggesting that marein can potentially prevent DN by suppressing renal SGLT2 expression.[22]

Osteoclastogenesis

Biological effect of marein on RAW264.7 cells by CCK-8 assay has been investigated to determine its effect on osteoclastogenesis. Marein inhibited lipopolysaccharide (LPS)-induced osteoclast formation by osteoclast precursor RAW264.7 cells. The effect of marein was related to its inhibitory function on expressions of pro-inflammatory cytokines and osteoclast-related genes containing RANK, TRAF6, MMP-9, CK, and CAII. Additionally, marein leads to markedly inhibited NF-κB signaling pathway activation in LPS-induced RAW264.7 cells. Marein could inhibit LPS-induced osteoclast formation in RAW264.7 cells via regulating the NF-κB signaling pathway which might be a potential drug for bacteria-induced bone destruction disease.[24]

Pancreatitis

Biological effects of flavonoids isolated from *Coreopsis tinctoria* on experimental acute pancreatitis (AP) have been investigated to explore the potential molecular mechanism. Freshly isolated mouse pancreatic acinar cells were treated with taurocholic acid sodium salt hydrate with or without flavonoids. Total flavonoids extract and flavonoids 1-6 (C1-C6) exhibited different capacities in reducing necrotic cell death pathway activation. Flavonoid C1 from *Coreopsis tinctoria* was protective in experimental AP and this effect may at least in part be attributed to its antioxidant effects by activation of Nrf2-mediated pathways. These results suggest the potential utilisation of *Coreopsis tinctoria* to treat AP.[30]

Renal Fibrosis

The protective mechanism of *Coreopsis tinctoria* and marein, the main ingredient in *Coreopsis tinctoria* on renal fibrosis and inflammation under HG conditions has been investigated using a HG-induced barrier dysfunction model in rat mesangial cells (HBZY-1). Marein suppressed rat mesangial cell hyperplasia and significantly attenuated the expression of HG-disrupted fibrotic and inflammatory proteins in HBZY-1 cells. Marein remarkably attenuated HG-induced renal inflammation and fibrosis by regulating the AMPK, TGF-β1/Smads, and NF-κB signaling pathways. Marein may delay the progression of DN, by suppressing HG-induced renal inflammation and fibrosis.[31] Content of marein in *Coreopsis tinctoria* extracts was determined by high-performance liquid chromatography-ultraviolet detection (HPLC-UV) and the radical scavenging capacity evaluated by the DPPH method. After three weeks of oral treatment with *Coreopsis tinctoria* extract (500 mg/Kg/day) the animals were no longer glucose-intolerant ($p>0.05$). *Coreopsis tinctoria* flowering tops infusion is able to abolish the streptozotocin-induced glucose-intolerance in rats after three weeks of oral treatment by a mechanism other than induction of insulin secretion.[32]

Intestinal Absorption

The absorption of total flavonoids from *Coreopsis tinctoria* in different intestinal segments was investigated by rat everted intestinal sac model. Marein from *Coreopsis tinctoria* were selected to evaluate the absorption characteristics of each component in different intestinal segments. The results showed that the absorption of seven components of total flavonoids at different intestinal segments was in consistent with zero order absorption rates. The K_a of marein showed weak concentration dependence. Marein was mainly absorbed in ileum. The total flavonoids of *Coreopsis tinctoria* are selectively absorbed in intestinal tract, the rat everted intestinal sac model can be used to evaluate the multi-component intestinal absorption characteristics of total flavonoids from *Coreopsis tinctoria*.[33]

Antioxidant

The chemical composition, antioxidant properties of snow chrysanthemum polyphenols (SCPs) and their effects on human intestinal microbiota were investigated. Five assays were used to investigate the antioxidant activities of SCPs. Subsequently, the effects of SCPs on intestinal microbiota *in vitro* were determined by high throughput sequencing and bioinformatics analysis. Marein was the major phenolic compounds, which accounted for 42.17%, 19.53% and 12.25%, respectively. Marein exhibited higher scavenging capacities in DPPH (EC_{50} = 8.84 μg/mL) and super anion radical assay (EC_{50} = 282.1 μg/mL). SCPs exhibited antioxidant properties and potential prebiotic effects on modulating the gut microbiota composition.[34] A simple and efficient method based on high-performance thin-layer chromatography coupled with 2,2-diphenyl-1-picrylhydrazyl (DPPH) bioautography (HPTLC-DPPH) was established for the screening and comparison of antioxidants in different parts of *Coreopsis tinctoria* herbal tea from different origins and other related herbal tea materials. Seven compounds made up the major contri-

butions of antioxidant activity in *Coreopsis tinctoria*, including marein. The established method could be applied for the identification of *Coreopsis tinctoria*, and were beneficial for the bioactivity-based quality control of *Coreopsis tinctoria*.[35]

Cytoprotective

The protective effect of *Coreopsis tinctoria* flowering tops aqueous extract, AcOEt fraction and the pure compounds marein and flavanomarein, against beta-cell injury has been investigated in a mouse insulinoma cell line (MIN6) challenged with pro-oxidant tert-butyl-hydroperoxide (tBHP) or cytokines. *Coreopsis tinctoria* flowering tops extracts (25-100 µg/mL) and pure compounds (200-400 µM), did not present any cytotoxicity. Treatment with this pro-oxidant also showed a rise in superoxide radical anion formation in MIN6 cells. This increase was significantly reduced by treatment with superoxide dismutase enzyme (SOD). Caspase 3/7 activation measurements show that *Coreopsis tinctoria* flowering tops extracts, as well as marein and flavanomarein, significantly inhibit apoptosis. *Coreopsis tinctoria* extracts and pure compounds show cytoprotection that seems to be due to inhibition of the apoptotic pathway.[36]

Epidermal Growth Factor

Biological effect of vhalcone and seven chalcone derivatives were used to analyse the relationship between the structure of these compounds and their inhibitory potential on tyrosine kinase activity. Three of chalcone derivatives, including marein were found to have an ability to inhibit the tyrosine kinase activity of epidermal growth factor receptor (EGFR) *in vitro*. IC50 was found to be 19 microM for marein. The inhibition of EGF-induced EGFR tyrosine phosphorylation by butein was also observed in human hepatocellular carcinoma HepG2 cells, while marein and phloretin were inactive at the doses tested. Molecular modelling suggests that marein can be docked into the ATP binding pocket of EGFR.[37]

Metabolic Profile

A rapid and systematic method based on ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS/MS) has been developed to detect metabolites of marein in plasma and urine after oral administration and injection. Sixty-one metabolites were identified and the metabolites are formed through a wide range of metabolic reactions, including hydroxylation, glucuronidation, methylation, hydrolysis, and desorption of hydrogen. The liver microsome incubation was further used to investigate the metabolic rate of marein. Network pharmacology was applied to study the targets and pathways of marein and its metabolites. Marein and its metabolites act on the same targets to enhance the therapeutic effect.[23]

Analytical Aspects

Liquid chromatography mass spectrometry (LC-MS) has been used to identify the main components in Fractions A-2-2 and A-2-3 of *Coreopsis tinctoria* Nutt. flower. LC-MS data showed that fraction A-2-2 and Fraction A-2-3, contain more than 10 components, including marein.[38] Marein should be used as a marker for the quality control of *Coreopsis tinctoria*.[39] A high performance liquid chromatography coupled with diode array detection and mass spectrometry (HPLC-DAD-MS) and 2,2'-azinobis(3-ethylbenzthiazoline-sulfonic acid) diammonium salt (ABTS) based assay was employed for identification of antioxidants in different samples of snow chrysanthemum. Fourteen peaks with antioxidant activity were identified, including the peak for marein.[40] Thirteen compounds, including flavanone and chalcone flavonoidal type have been identified in fraction by HPLC-DAD-ESI-MS/MS, and the major one was found to be marein in *Coreopsis tinctoria* Nutt. which was further quantified by HPLC-UV.[41] A simple and reliable high-performance liquid chromatography coupled with diode array detection method has been used for the quantitative analysis and comparison of major phytochemicals in *Chrysanthemum morifolium*, *Florists chrysanthemum* and snow chrysanthemum (*Coreopsis tinctoria* or *Coreopsis tinctoria*). The chromatographic separation was achieved on a reversed phase C18 column with a mobile phase of water [containing 0.1% trifluoroacetic acid (TFA)] and acetonitrile. *Coreopsis tinctoria* possessed the highest amount of flavonoids, including marein. The marein content in *Coreopsis tinctoria* was as high as 36.50 mg/g. Further, the content of marein in *Chrysanthemum morifolium* was slightly higher than that in *Florists chrysanthemum*.[42] A simple, accurate and reliable high performance liquid chromatography coupled with photodiode array detection (HPLC-DAD) method was developed and then successfully applied for simultaneous quantitative analysis of eight compounds, including marein in 23 batches of snow chrysanthemum of different seed provenance and from various habitats.[43] A combination of chemical partitioning and molecular fingerprinting was used for the unequivocal identification of commercial *Pistacia vera* L. seed varieties (Bronte, Kern, Kerman, Larnaka, Mateur and Mawardi) of different geographical origin. The total phenolic content was higher in the variety Bronte followed by Larnaka and Mawardi cultivars. HPLC-DAD-ESI-MS/MS analyses revealed significant amounts of marein in the variety Bronte.[44] Several polyketide-based inhibitors against the *Enterococcus faecalis* shikimate pathway enzyme, 3-dehydroquinate dehydratase (DHQase) have been identified. In particular, marein inhibited DHQase and retarded the growth of *Enterococcus faecalis* which provides a route in the development of polyketide-based antimicrobial inhibitors targeting the shikimate pathway of the human pathogen *Enterococcus faecalis*.[45] Marein has been isolated from the

leaves of *Bidens pilosa* L. and their chemical structures have been elucidated by spectroscopy.[46] Three new phenolic compounds, together with nine known compounds, including marein, were isolated from the buds of *Coreopsis tinctoria* Nutt. The chemical structures of these compounds were elucidated by extensive spectroscopic analysis and on the basis of their chemical reactivity.[47] The chemical characteristics of different parts (flowers, buds, seeds, stems, and leaves) of *Coreopsis tinctoria* were investigated based on microwave-assisted extraction and the simultaneous determination of 13 major active compounds by high-performance liquid chromatography, including marein.[48] Quantitative analysis multi-components by single marker were used to test the cumulative absorption volume Q, absorption rate constant Ka, and apparent permeability coefficient Papp of the four main ingredients in *Coreopsis tinctoria* Nutt. extract, in different intestinal segments in rats using a Ussing chamber model and high-performance liquid chromatography. Papp of marein in the duodenum and jejunum was <1.0×10(-6), and was 1.0×10(-6) to 10×10(-6)cms(-1) in the ileum and colon. All four chemical components of the plant extract can be absorbed by the intestinal canal of rats, and the ileum presented the best absorption.[59]

Table 1. Biological source of marein from natural sources

S. No	Biological source	Reference
1.	*Coreopsis tinctoria*	[38,39,41,42,47–49]
2.	*Chrysanthemum morifolium*	[42]
3.	*Florists chrysanthemum*	[42]
4.	*Pistacia vera*	[44]
5.	*Bidens pilosa*	[46]

Conclusion

In the present paper we have collected all the scientific information of marein and presented in this review article in order to know the therapeutic value of marein in medicine. Scientific information of marein for their biological activities has been searched in Google, Google Scholar, PubMed, Scopus, and Science Direct and collected scientific information of marein were presented here in this review article. All the collected scientific information of marein has been analyzed in the present review paper in order to know the health beneficial aspects of marein. Therapeutic potential of *Coreopsis tinctoria* were also discussed here in very concise manner in the present work in order to understand the biological importance of marein in medicine as marein is one of the main phytochemical of *Coreopsis tinctoria*. Further, the detail pharmacological activity of marein was analyzed in the present review paper. Analytical aspects of marein were also included in the present review paper to understand the biological source of marein in the nature and their analytical parameters for their estimation in different samples (Table 1). Present paper scientific data described the biological importance and therapeutic potential of marein for their effectiveness in SARS-CoV-2,

Table 2. Molecular mechanism of marein in medicine

S. No	Biological activities	Molecular mechanism	Reference
1.	Diabetic nephropathy	Marein improves DN by inhibiting renal SGLT2 and activating p-AMPK. This suggests that marein may be able to prevent DN by directly suppressing SGLT2 expression in the kidney.	[22]
2.	Osteoclastogenesis	Marein inhibits LPS-induced osteoclastogenesis in RAW264.7 cells by NF-κB signaling pathway. Scientific data suggest that marein has the potential to be a treatment for bone-destructive diseases caused by bacteria. Results provide new information on LPS-induced bone disease.	[24]
3.	Glucose level	Marein can enhance aberrant glycolipid metabolism in hypertrophic H9c2 cells, and this effect may be explained by the reduction of HIF-1α expression and subsequent regulation of PPARα/γ-mediated adipogenic gene expression.	[25]
4.	Intervertebral disc degeneration (IDD)	Marein protected HNPCs from HG-induced damage and ECM degradation, at least in part, by inhibiting the ROS/NF-κB pathway.	[21]
5.	Hypoglycemic agent	Marein induces hypersensitivity in HepG2 cells through CaMKK/AMPK/GLUT1, which promotes glucose uptake, IRS/Akt/GSK-3β, which increases glycogen synthesis, and Akt/FoxO1, which decreases gluconeogenesis. Improved glucose-induced insulin resistance. Marein may be a promising compound in the development of hypoglycemic drugs.	[19]
6.	Diabetic encephalopathy (DN)	The neuroprotective effects of marein are due to reduced damage to mitochondrial function and activation of the AMPK signaling pathway. These results indicate that marein may be a powerful compound to prevent/counter diabetic encephalopathy.	[29]
7.	Renal fibrosis	Marein may delay the progression of DN, at least in part, by suppressing HG-induced renal inflammation and fibrosis.	[31]

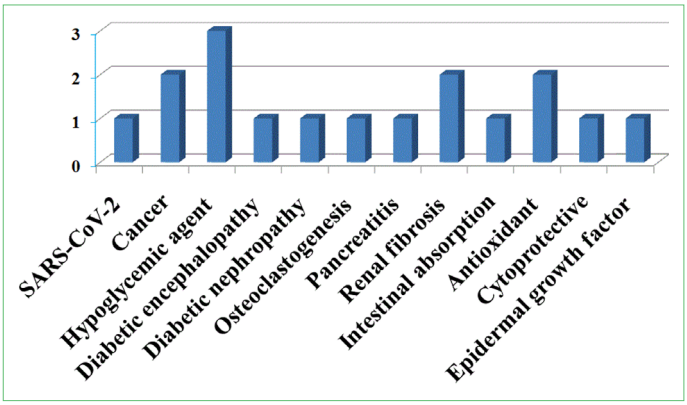

Figure 1. Pharmacological activities of marein.

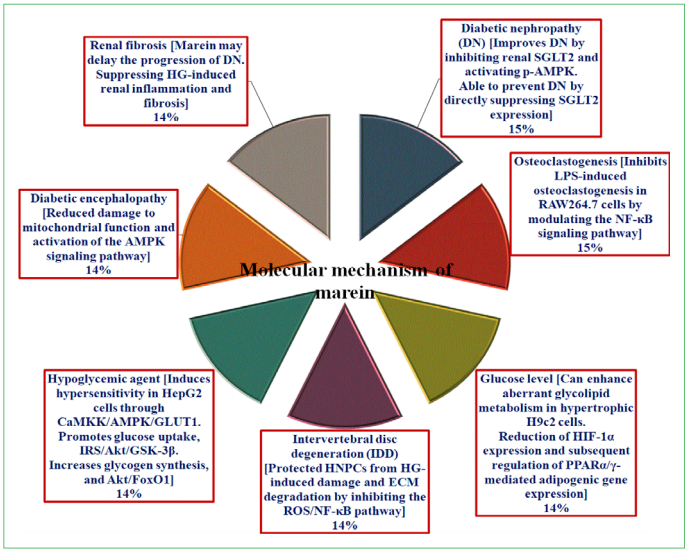

Figure 2. Molecular mechanism of marein for their different pharmacological activities.

cancer, hyperglycemia, diabetic encephalopathy, diabetic nephropathy, osteoclastogenesis, pancreatitis and renal fibrosis. Further present paper also described their intestinal absorption, antioxidant, cytoprotective potential with their effect on epidermal growth factor (Fig. 1). Further different molecular mechanism responsible for these pharmacological activities was also presented in the Table 2 and Figure 2. However the analytical techniques of marein for its separation, isolation and identification of in various samples were also described in the present paper. Present work will be beneficial for all the researchers to know the biological importance and therapeutic potential of marein.

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