Phytochemicals and Human Health

10

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Abstract

The World Health Organization (WHO) defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." Any disturbance in this well-being leads to ill-health and a related condition called pathophysiology. Disease conditions, xenobiotics, and environmental and social stresses are the most common causes behind these pathophysiological conditions, and this can be generalized from recent studies that in most of the cases ROS plays the pivotal role as the main effector. However, fortunately in many cases, these health problems are preventable. Reasonable cost, presence in the daily consumables, and negligible side effects make the naturally occurring plant-derived compounds interesting and attractive for pharmacological study in recent years. Primarily for the defense purpose, plants yield assorted types of low-molecular-weight products. These are generally termed as phytochemicals. Among them, a group of secondary metabolites associated with a polyphenolic group have been named flavonoids and are of pronounced interest due to their implausible pharmacological properties. Flavonoids are widely accepted as potent antioxidant agents which can prevent injury caused by free radicals by scavenging of ROS, activation of antioxidant enzymes, and inhibiting oxidases. In addition, increase in antioxidant properties of low-molecular antioxidants, metal chelating activity, and reduction of α-tocopheryl radicals and mitigation of oxidative stress caused by NO also plays important role. In this chapter, we have summarized most of the findings, if not all, available till date related to five very noticeable phytochemicals, namely, morin, quercetin, rutin,

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mangiferin, and myricetin. Hope this chapter will help readers in understanding the utmost importance of the phytochemicals and will motivate them to further dig into the mechanistic study to fetch more novel information.

Keywords
Phytochemicals · Morin · Quercetin · Rutin · Mangiferin · Myricetin

10.1 Introduction

Rational cost, present mostly in consumables, and negligible side effects make the naturally occurring compounds fascinating and attractive for pharmacological study in recent years. Plants yield diverse types of low-molecular-weight products mainly for the defense purpose. Among them, a group of secondary metabolites associated with a polyphenolic group have been named flavonoids and are of pronounced interest due to their implausible pharmacological properties. The term flavonoid is derived from the Latin word "flavus," meaning yellow. These are phenolic substances show various biological activities like antiallergenic, anti-inflammatory, antiviral, gastroprotective, cardioprotective, renoprotective, neuroprotective, vasodilating actions, etc.[1]. Approximately, more than 3000 varieties of flavonoids have been recognized. The flavonoids consist of six major subgroups, namely, flavone, flavonol, flavanone, chalcone, anthocyanins, and isoflavonoids. Along with carotenes, flavonoids are responsible for the coloring of fruits, herbs, and vegetables. The most significant dietary sources are fruits, soybean, and tea, where green and black tea contains as much as about 25% flavonoids. Other important sources of flavonoids are citrus fruits (rutin and hesperidin), apple (quercetin), flowers, red wine, nuts, herbs, vegetables, fruits, seeds, spices, stems, etc.

The concept of oxidative stress or the imbalance between prooxidants and antioxidants in a living system has been comprehensively associated with the biomedical sciences since last two decades. Oxidative stress plays a significant role in the pathophysiology of highly prevalent diseases such as hypertension, diabetes, acute renal failure, atherosclerosis, Alzheimer's, Parkinson's diseases, etc. In typical physiological conditions, ROS are unceasingly produced and are excellently removed by several antioxidant defense systems (e.g., antioxidant proteins, enzymes, vitamins, etc.). However, an increased ROS levels in the cell have a considerable impact which leads to defective cellular functions, disease, and aging.

Flavonoids are widely accepted as potent antioxidant agents which can prevent injury caused by free radicals by scavenging of ROS, activation of antioxidant enzymes, and inhibiting oxidases. In addition, increase in antioxidant properties of low-molecular antioxidants, metal chelating activity, and reduction of α-tocopheryl radicals plays an important role.

This chapter aims to present a brief idea of the beneficial role of naturally occurring phytochemicals (Table 10.1) in relation to human health. It is believed that this will inspire readers and researchers in the field of applied pharmacology, ethnobotany, and other related fields of research. Here we would like to discuss the

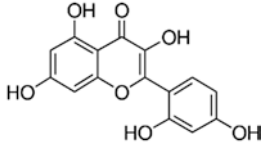
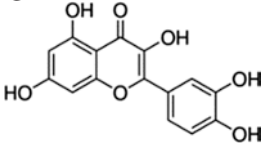
beneficial efficacy of several important flavonoids in the light of numerous up-to-date reports.

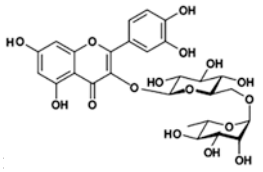
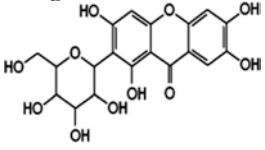
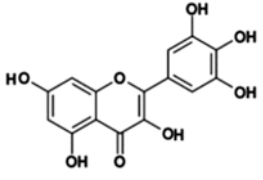
10.2 Morin

Morin [morin hydrate: 2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one hydrate, 2′,3,4′,5,7-Pentahydroxyflavone] belongs to the group of flavonols found regularly in the branches of the family members of Moraceae like Osage orange (*Maclura pomifera*), white mulberry (*Morus alba* L.), fig (*Chlorophora tinctoria*), almond (*Psidium guajava*), mill (*Prunus dulcis*), old fustic (*Maclura tinctoria*), etc. [2, 3]. Morin exhibits different types of pharmacologically important properties like free radical scavenging activity, anti-inflammatory property, xanthine oxidase inhibitor property, gastroprotective property, hepatoprotective property, anticancer property, etc. It also possesses several add-on health benefits. Also, an accumulative number of studies showed that morin suggestively modulates different cell signaling pathways related to chronic pathophysiological conditions. We will discuss few of them in the following section.

Excitotoxicity (i.e., excessive glutamate receptors activation) leads to acute and chronic neurological disorders including stroke**.** In vitro model of excitotoxic neuronal death involving NMDA receptor over activation has already showed the neuroprotective role of morin [4]. In PC12 neuronal differentiated cells, Zhang et al. showed the neuroprotective role of morin on 1-methyl-4-phenylpyridinium ion-mediated apoptotic cell death as well as in an in vivo model (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced murine model of Parkinson's disease). They found that upon addition of morin in the system, there was a significant attenuation of the MPP + −induced loss of cell viability, apoptosis, and inhibition of ROS formation in the in vitro model, whereas morin significantly attenuated the MPTP-induced dopaminergic neuronal death, nigrostriatal lesions, striatal dopamine depletion, and permanent behavioral deficits in vivo [5]. In another study, Subash and Subramaniam evaluated the chronotherapeutic effect of morin on ammonium chloride (AC)-induced hyperammonemia using rat model. Ammonia is considered as a persuasive neurotoxin. It has been strongly associated in the pathogenesis of hepatic encephalopathy. In hyperammonemic rats, the chronotherapeutic role of the molecule was suggested due to the temporal variations of antioxidants, lipid peroxidation, urea cycle enzymes, metabolic enzymes involved in morin degradation, and the temporal variation in the bioavailability of morin [6].

Table 10.1 Depicts the chemical structure, nature, as well as the biological properties of morin, quercetin, rutin, mangiferin, and myricetin

Name of the molecule and structure	Molecular formula	Molar mass	IUPAC name	Solubility	Biochem/physiol actions
	$C_{15}H_{12}O_8 . {}_XH_2O$	302.24 g Mol^{-1}	2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one;hydrate	Methanol (50 mg/ml); water (0.25 mg/ml, 20 °C; 0.94 mg/ml, 100 °C); aqueous alkaline solutions; ether and acetic acid (sparingly soluble)	Free radical scavenging activity, anti-inflammatory property, xanthine oxidase inhibitor property, gastroprotective property, hepatoprotective property, anticancer property, etc.
Quercetin 	$C_{15}H_{10}O_7$	302.238 g Mol^{-1}	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	Very soluble in ether, methanol; soluble in ethanol, acetone, pyridine, acetic acid; soluble in alcohol and glacial acetic acid; in water, 60 mg/L at 16 °C	Cardiovascular protection, antiviral, anti-inflammatory activity, antitumor, anticancer, anti-ulcer, anti-allergy, antidiabetic, gastroprotective effects, antihypertensive, immunomodulatory, anti-infective, etc.

	$C_{27}H_{30}O_{16}$	610.521 g Mol^{-1}	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl] oxan-2-yl] oxychromen-4-one	Pyridine solubility: 50 mg/mL; DMSO: Soluble; aqueous base: Soluble; water solubility 125 mg/L	Antimicrobial, antifungal, antiallergic properties, free radicals scavenging activity, antidiabetic, neuroprotective effects, etc.
Mangiferin 	$C_{19}H_{18}O_{11}$	422.342 g Mol^{-1}	1,3,6,7-tetrahydroxy-2-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]xanthen-9-one	Solubility: 20 mg/mL DMSO	Antistimulatory, antimodulatory, antioxidative, antidiabetic, dyslipidemic, antiallergic, analgesic, anticancer, anti-HIV properties, etc.
Myricetin 	$C_{15}H_{10}O_8$	318.237 g Mol^{-1}	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one	Sparingly soluble in boiling water; soluble in alcohol	Anti-inflammatory, antioxidant, antidiabetic, anticancer, iron-chelating activities, etc.

A contemporary study was conducted to assess the antiarthritic effect of an ethanolic extract of *Ficus exasperata* (FEE) in an arthritis rat model in which the arthritis was induced by the Freund's adjuvant and dexamethasone and methotrexate were used as positive controls [7]. Along with these positive controls, FEE also showed significant antiarthritic properties by preventing the arthritic edema in the lateral paw of the animals and also the spread of the edema from the lateral to the contralateral paws. The principal active compound in the FEE is believed to be the morin. Zeng et al. also found morin effective against type II collagen-induced arthritis (CIA) in rats in terms of attenuating arthritic development specified by reduction of paw swelling and arthritis scores [5]. Sultana and Rasool ascertained the effectiveness of morin-NSAID combinatorial therapy in subduing the pathogenesis of rheumatoid arthritis (RA) in rats where they found that imbalances in the paw edema, levels/activities of elastase, inflammatory mediators (TNFα, IL1β, PGE2, VEGF, and MCP1), glycoproteins (hexosamine and hexose), urinary constituents (hydroxyproline and glycosaminoglycans), reactive oxygen species (LPO and NO), proinflammatory cytokines (IL1β, TNFα, IL17, MCP1, and IL6), inflammatory enzymes (iNOS and COX2), RANKL, and transcription factors AP1 and NFkB p65 were elevated in case of RA whereas regulated back effectually to the basal level by morin and indomethacin [8].

Morin also have efficient gastroprotective activity. In a study, we have shown that morin considerably ameliorates nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathyin SD rats. We found that the gastroprotective action of morin is primarily accredited to its persuasive antioxidant and anti-inflammatory nature[1]. In another study, Galvez et al. reported that morin possesses intestinal anti-inflammatory activity. They found that colonic insult with trinitrobenzenesulfonic acid induces myeloperoxidase activity, colonic leukotriene B4 and IL-1β levels, oxidative stress, and colonic nitric oxide synthase activity, whereas morin effectively reduces the changes [9]. Morin hydrate also has been shown to constrain nitric oxide synthase activity and the leukotriene B4 synthesis [10].

Cardiovascular diseases (CVD) are the main cause of chief death worldwide due to its byzantine nature. Among CVD, myocardial infarction (MI) is a foremost one. Al-Numair et al. showed that morin protects cardiovascular system in isoproterenol-induced myocardial infarction by chiefly scavenging free radicals [11]. They suggest that morin supplement on a daily basis significantly decreases the activities of cardiac marker enzymes such as lactate dehydrogenase, aspartate transaminase, creatine kinase, and creatine kinase-MB in serum. They also showed that the activity of sodium-potassium-dependent adenosine triphosphatase was decreased, whereas calcium-dependent adenosine triphosphatase and magnesium-dependent adenosine triphosphatase were found to increase in the heart as well as the levels of glycoprotein containing hexose, hexosamine, fucose, and sialic acid decreased both in the heart and serum. Prahalathan et al. recently proved the protective effect of morin against deoxycorticosterone acetate (DOCA)-induced hypertension in male Wistar rats where they showed that the morin effectively lowered the increased systolic and diastolic blood pressure in association with considerably increased systolic

and diastolic blood, ALT, GGT, AST, ALP, urea, uric acid, and creatinine levels in the plasma of hypertensive rats [12].

Morin also has significant effect on diabetes and related pathophysiology. Noor et al., from transmission electron microscopy (TEM) and right-angle light scattering, showed that morin hydrate inhibits amyloid formation by human islet amyloid polypeptide (IAPP, amylin), and not only that it even disaggregates preformed IAPP amyloid fibers [13]. IAPP is related to the formation of amyloid in islets in type 2 diabetes and in the transplantation of islet cell which in turn leads to graft failure. Human IAPP is extremely amyloidogenic and has fewer inhibitors, whereas specific substitution pattern on the B-ring makes morin hydrate a novel type of IAPP amyloid inhibitor [3, 13]. Vanitha et al. observed that morin administration resulted in significant reduction in blood glucose levels, an increase in the levels of serum insulin in type 1 diabetic experimental rats [14]. Morin dose-dependently ameliorated the altered levels of glucose-6-phosphate dehydrogenase, fructose-1,6-bisphosphatase, glucose-6-phosphatase, and hexokinase in the liver and significantly preserved insulin-positive cells as well as protected the overall morphology in the pancreatic islets of diabetic rats [14]**.** Abuohashish et al. found that both the anti-inflammatory and antioxidant properties of morins are useful against diabetic osteopenia in rats [15]. A study showed that when morin was administered in diabetic rats, there was a significant attenuation of bone loss which was evident at bone turnover parameters level which included BALP, OC, CTX, and DPD [15]. They also found that morin brings back the changes occurred in diabetic rats in respect to serum levels of glucose, TBARS, IL-1β, IL-6, TNF-α (which were significantly elevated), and that of insulin and GSH (which were decreased) [15].

Besides the abovementioned activity, morin also possesses significant immunoregulatory activity. In an independent study, Kim et al. showed that morin repressed IgE-mediated allergic responses by inhibiting production of IL-4 and TNF-α and degranulation of antigen (Ag)-stimulated mast cells in a mice model. They also found that morin inhibited the phosphorylation of spleen tyrosine kinase (Syk) (which plays a very important role in the Syk activation) and activation of linker for activation of T cells (LAT) in rat bone marrow-derived mast cells (BMMCs) and basophilic leukemia (RBL)-2H3 cells, along with the inhibition of p38, Akt, and MAPKs. Their results suggest that inhibition of Fyn kinase in mast cells by the morin is mainly responsible for the action described above [16]. The notion is also supported by the findings of Fang et al. which indicated that morin might have the ability to regulate immune response through modulating the cytokine profiles displayed in chronic immunotoxic pathophysiology where they have shown that morin and it's sulfated or glucuronidated derivatives were operative on LPS-activated RAW 264.7 cells by tumbling NO, TNF-α, and IL-12 production. They also showed the reduced phagocytic activity of peripheral blood cells in the morin-treated cells in respect to control. These activities such as reduced macrophagic phagocytic activities, lowering of NO production, etc. resembled to LPS-resistant state, and this is very important to treat various chronic autoimmune diseases [17].

Morin exlung parenchyma and airways isatocytes against chemically produced rat tongue carcinogenesis and blocked phorbol ester-mediated transformation

[18, 19]. Besides, it inhibited the lipoxygenase pathway and the peroxisome proliferator-activated receptor-mediated differentiation of keratinocyte [3, 20]. In context to the release of inflammatory cytokines from mast cells such as IL-6, IL-8, TNF, etc., the inhibitory role of morin was reported [21]. Morin hydrate exhibited anticancer activity in an in vivo study, i.e., in cancer models (viz., inhibition of COLO205 cells growth in nude mice) [22]. Morin hydrate downregulated NF-κB which in turn inhibited the inflammatory gene cascade along with the downregulation of several factors related to NF-κB which take part in cell survival such as X-chromosome-linked IAP, inhibitor of apoptosis protein 1 and 2 and BcL-xL, in cell proliferation, viz., cyclooxygenase-2 and cyclin D1, and invasion such as matrix metalloproteinase-9 [3, 23].

From the diverse studies reviewed here, morin emerged as a valuable natural flavone in the management of different chronic pathophysiological conditions. Different studies also showed that it could be used as an exceptional and novel pathological detection tool. Nevertheless, in future more studies are required on the morin in understanding the precise molecular mechanism of its action and to discover new possibilities.

10.3 Quercetin

Quercetin is one of the significant bioflavonoids present in many medicinally important plants and has numerous beneficial effects including cardiovascular protection, antiviral, anti-inflammatory activity, antitumor, anticancer, anti-ulcer, anti-allergy, antidiabetic, gastroprotective effects, antihypertensive, immunomodulatory, anti-infective, etc.[24, 25, 26]. Quercetin has also proved to be beneficial against environmental stress which causes formation of free radicals such as smoking and pollution [27, 28].

The name quercetin (3,3′,4′,5,7-pentahydroxyflavone) is derived from the Latin word “quercetum” that means oak forest. It fits in to the class of compounds called flavonols [24]. The compound is yellow in color and quite soluble in alcohol and lipids where as poorly soluble in hot water and virtually insoluble in cold water. This dietary flavonoid is mainly found in citrus fruits, seeds, green leafy vegetables, nuts, olive oil, apples, broccoli, barks, green tea, onions, red grapes, red wine, berries, dark cherries, buckwheat, cranberries, blueberries, etc. [27].

Researchers have shown the impact of quercetin as systemic anti-inflammatory agents [29]. Elevated C-reactive protein (CRP) levels are associated with numerous diseases states which involve inflammatory conditions, whereas intake of quercetin can lower the levels of the inflammatory risk factor, CRP. In preclinical in vitro studies, García-Mediavilla et al. showed that quercetin significantly reduces the levels of inflammatory mediators such as COX-2, NO synthase, and CRP in human hepatocyte-derived cell line [30]. Whereas, quercetin, in a dose-dependent manner, inhibited both acute and chronic inflammation related to arthritis and also showed significant antiarthritic activity against adjuvant-induced arthritis, in murine models [31, 32].

In a study including human as a model, Askari et al. found that 2-month quercetin supplementation (at a dose of 500 mg) in healthy male nonprofessional athletes with consistent workout showed a significant decrease in the levels of CRP, [whereas, quercetin remain ineffective (at a dose of 500 mg/day) in altering the levels of CRP in female patients, with rheumatoid arthritis (RA)[27, 33, 34]]. But in another study it has been shown that xanthine oxidase inhibition activity of quercetin make it able to prevent the accumulation of uric acid, which may help the subjects who are suffering from gout[35].

Quercetin also possesses a wide spectrum of biological activities which may have a positive influence on cardiovascular diseases. A study on 30 men suffering from coronary heart disease (CHD) showed that the consumption of red grape polyphenol extract rich in quercetin caused an increase in flow-mediated dilation of major arteries, which in fact a persuasive indicator of improved endothelial health [36]. The molecule inhibited the aggregation of platelets and improved the endothelium. It protected against CHD and reduced the mortality risk caused due to low-density lipoprotein (LDL). The molecule exhibited a vasorelaxant effect on isolated arteries which in turn helped in lowering blood pressure and prevented the cardiac hypertrophy onset [27, 37]. Quercetin prevented LDL and cholesterol damage, and in context to this, it was observed that consuming high flavonoid containing food supplements could lower cholesterol. It was observed that LDL oxidation was inhibited on consumption of quercetin along with an alcohol-free red wine extract containing quercetin [38]. In a 6-week clinical trial, quercetin reduced oxidized LDL levels in plasma and systolic blood pressure in subjects who were at high risk of heart disease [39]. Quercetin has a feature to induce apoptosis in mature fat cells while inhibits fat accumulation in maturing human fat cells [40, 41]. It also blocks the uptake of glucose from the blood and the fat cell production while enhances the fat cell necrosis [27, 42, 43].

Neuro-inflammatory processes in the central nervous system are the ultimate fate of neurodegenerative diseases such as Alzheimer's and Parkinson's disease as well as neuronal injury associated with stroke [44]. Quercetin and ascorbic acid combinatorial therapy effectively reduces the incidence of oxidative damage to neurovascular structures in the skin and prevents damage to neurons. Quercetin is also capable to protect brain cells against the oxidative stress-induced tissue damages which sequentially leads to Alzheimer's and other neurological conditions [24, 27].

The anticancer effect of quercetin includes the suppression of antiproliferative growth factor and antioxidant [45]. It possesses anticarcinogenic property and also acts as an apoptosis inductor; decreases the tumor growth of colon, liver, brain, and other tissues; and restricts the spread of malignant cells [46, 47]. Combination therapy of quercetin along with curcumin decreased both the size and number of rectal and ileal adenomas with minimal and/or no adverse effects [48].

Quercetin inhibits chemical carcinogen, hexavalent chromium (Cr[VI]), induced cell transformation, ROS generation, and MicroRNA-21 (miR-21) elevation in human colon cancer Caco-2 cells [27, 49, 50]. It also has beneficial effect on prostate cancer which was proved through in vitro and in vivo cancer studies [51].

Quercetin also has significant gastroprotective activity. It can inhibit lipid peroxidation and gastric acid secretion of gastric cells, and in doing so, it can serve as a gastroprotective agent. *Helicobacter pylori* infection, a potent ulcer forming agent, can also be inhibited by quercetin [24]. Suzuki et al. showed that quercetin dose-dependently inhibits ethanol-induced gastric mucosal injury in rats. The results suggest the anti-ulcer activity of quercetin through its free radical scavenging activity or its enhanced production in gastric mucus [52, 53].

The molecule exhibited anti-allergy effect by inhibiting histamine release from the mast cells and several allergic molecules and in the prevention of bronchitis and asthma [27, 54].

Progressive chronic inflammatory disorder of lung parenchyma and airways is collectively known as chronic obstructive pulmonary disease (COPD). However, unfortunately, therapies for COPD are said to be partially effective with opportunities of side effects. But as a hope, recent evidences are showing that the quercetin supplementation is beneficial in COPD. It has been shown previously that a fourfold increase in plasma quercetin levels ominously decreased lung inflammation and prevented the disease progression. Perhaps the anti-inflammatory property of quercetin is attributed to its beneficial role in pulmonary disorders [55]. Also a clinical trial of 12 weeks duration proved quercetin (at a dose of 1000 mg/day) beneficial against upper respiratory tract infection rates in middle- and older-age patients [56].

10.4 Rutin

Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonoid that is prevalent in the plant kingdom [57]. Rutin has a wide range of pharmacological properties. It has widely been exploited as human medicine and nutrition. It has proved to have antimicrobial, antifungal, and antiallergic properties and hence widely used as alternative medicine. However, current research has shown its multispectrum pharmacological benefits for the treatment of various chronic diseases, such as cancer, diabetes, hypertension, and hypercholesterolemia [58]. Recently, Patil et al. showed the potential of rutin in alleviating the radiation-induced cytogenetic damage and mortality. They have speculated that the activity might be attributed to the free radicals scavenging activity of rutin [59, 60]. Park et al. showed that rutin has an osteoblast stimulant property. The study showed that it could induce bone development via the differentiation of human MG-63 osteosarcoma cells [61]. Rutin also has antidiabetic activity. It is potent for glycemic control by enhancing the activity insulin-mediated receptor kinase and thereby triggering the insulin pathway which in turn would increase both the translocation of glucose transporter 4 as well as glucose uptake [62]. From a study Niture et al. speculate that rutin inhibits inflammatory cytokines and also improves the antioxidant and plasma lipid profiles in high-fat diet. It also did the same in streptozotocin-induced type 2 diabetic model. Hence they projects rutin as a diabetic modulator together with customary antidiabetic drugs [59, 63]. Rutin has significant beneficial effects over several neurological disorders. It has been proven to protect against the neurodegenerative effects of

prion buildup by increasing the production of neurotropic factors and also by inhibiting apoptotic pathway activation in neuronal cells [64]. Nieoczym et al. showed that it also has a weak and temporary anticonvulsant effect [65]; whereas, Qu et al. showed that rutin has multi-target therapeutic potential for cognitive discrepancies related to conditions involving enduring cerebral hypoperfusion, such as Alzheimer's disease and vascular dementia [66]. Rutin was found to provide protection against trimethyltin-induced impairment of spatial memory and the involvement of dopaminergic system, as well as synaptophysin has been suggested in trimethyltin-triggered damage of neuronal cells in the hippocampus [59, 62, 61]. Rutin also can modulate NO production and thus can modulate NO-related physiological and/or pathophysiological processes. Ugusman et al. showed that rutin increases nitric oxide production in human endothelial cells and thus improved endothelial function [67].In ultraviolet B-irradiated skin of mouse, rutin exerted anti-inflammatory effects by interfering with the cyclooxygenase-2 expression as well as nitric oxide synthase production [68]. Rutin provided protection against high cholesterol diet-mediated hepatotoxicity and inflammation [69].

10.5 Mangiferin

2-*C*-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone or mangiferin ($C_{19}H_{18}O_{11}$) having a molecular weight of 422.35 and a melting point of 271 °C (anhydrous) is a naturally occurring *C*-glucoside xanthone. This xanthone derivative is obtained from the fruits, leaves, bark, and roots of *Mangifera indica* and belongs to Anacardiaceae family. Mangiferin has been reported to exhibit a diversified use in therapeutics. It possesses antistimulatory [70], antimodulatory [71], antioxidative [72, 73], antidiabetic, dyslipidemic, antiallergic, analgesic, anticancer, and anti-HIV properties [74–78].

Evidences suggest that mangiferin possesses iron-complexing ability which in turn is believed to be the mechanism for protection against Fe^{2+} citrate-mediated lipid peroxidation in rat liver [79]. Mangiferin, at a concentration of 10 μM, reflected amelioration against Fe^{2+} citrate-triggered swelling of mitochondria followed by loss of mitochondrial membrane potential. Iron citrate-triggered antimycin A-insensitive consumption of oxygen in mitochondria was found to be inhibited by the xanthone derivative. On the other hand, mangiferin induced oxygen consumption by stimulating Fe^{2+} autoxidation and prevented the reduction of Fe^{3+}ascorbate. The mangiferin-Fe^{2+}/Fe^{3+} absorption spectra suggested the possibility of transient charge transfer complex formation between mangiferin and Fe^{2+}, Fe^{2+} oxidation acceleration, and formation of a stable complex, i.e., Fe^{3+}-mangiferin complex. This complex fails to take part in Fenton-type reactions and propagation of lipid peroxidation, thus suggesting that the antioxidant activity of mangiferin is contributed due to its iron-chelating activity and is not contributed due to scavenging of free radicals. In this respect, the molecule has pharmacological relevance in terms of chelation therapy in diseases related to iron overload or abnormal distribution of intracellular iron [77].

Studies have revealed that in OF1 mice, mangiferin showed protection by restoring the altered levels of antioxidant enzymes, viz., superoxide dismutase, etc., prevented protein oxidation significantly in terms of the net sulfhydryl group protein content, reduced lipid peroxidation confirmed through 4-hydroxy-alkenals and malondialdehyde assays, checked the release of cytochrome *C*, and inhibited apoptotic cell death [72]. The strong antioxidant activity of mangiferin has been confirmed through 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay [80]. Even from the structural point of view, this property of the molecule is well understood as it possesses four phenolic H-atoms of which two can readily be involved in interacting with free radicals to form phenoxy radicals which in turn are resonance stabilized [77, 80].

Inflammation involves several mediator, viz., nitric oxide (NO), which is synthesized by NO synthase and prostanoids synthesis through cyclooxygenase (COX-2). Dilatation of arterioles occurs due to an increase in blood permeability and blood flow which is a vascular event of inflammation [81, 82]. Beltran et al. showed that in spontaneous hypersensitive and normotensive rats, mangiferin inhibited the IL-1β mediated induction of COX-2 and iNOS; however, no effect was exerted with the molecule in absence of IL-1β on iNOS and COX-2 of noradrenaline-mediated vasoconstriction from mesenteric arteries of vascular smooth muscle cells [83]. In activated macrophages, mangiferin significantly reduced the level of transcription of iNOS as well as the production of NO [84]. In regard to the anti-inflammatory mechanism of mangiferin, inhibition of NF-κB activation is believed to be involved which in turn regulates the activation of the promoter for iNOS and COX-2 genes [85].

NF-κB regulates the cascade of gene encoding inflammatory enzymes, proinflammatory cytokines, adhesion molecules, and chemokine which are overexpressed as a response to inflammation [86]. Evidence suggests that the activation of NF-κB is concomitantly associated with ROS production [87]. Mangiferin was observed to suppress the activation of NF-κB which in turn inhibits the inflammatory gene cascade, increased intracellular antioxidant levels, and triggered anticancer drug-mediated cellular death, indicating a plausible role as a combination therapy in treating cancer [88]. This ameliorative property of mangiferin is believed to be mediated through free radical quenching and increasing intracellular GSH which in turn interferes with TNF-mediated NF-κB activation [89]. Microarray data showed that magniferin countered NF-κB activation induced by IL-1, TNF, and LPS through TNF receptor-mediated factor 6; inhibited NF-κB triggered activation of signaling molecules, viz., RelA and RelB (genes of Rel/NF-κB/κB); and hindered the expression of toll-like receptors such as JNK1 and JNK2 in a thioglycollate-triggered murine macrophages elicited with gamma interferon and lipopolysaccharide model [71]. Mangiferin was also found to inhibit TNF-mediated protein synthesis.It also trigger DNA damage,apoptotic cell death, and inhibit an array of proinflammatory cytokines, viz., IL-1, IL-6, IL-1α, macrophage colony stimulating factors, adhesion molecules, etc. [71]. Studies hence revealed that mangiferin modulated the expression of an array of genes involved in regulating inflammation, apoptosis,

tumorigenesis, viral replication, and many others and thus depicting its immunomodulatory property.

Exposure to the industrial and environmental pollutant, Hg has been reported to affect the central nervous system and varied target organs, viz., the liver, kidney, gastrointestinal tract, etc. Evidences suggest that Hg(II) generates ROS through thiol complexation, peroxidizes lipid molecules of mitochondrial membrane which leads to a drop of mitochondrial membrane potential, interferes with the sulfhydryl (-SH) group, and hence results in depletion of intracellular thiols, e.g., GSH [90]. Hg(II) interferes with the conformation and activity of proteins through side-chain modifications and compromises the activities of antioxidant enzymes, viz., CAT, SOD, GST, GR, etc. [91]. These Hg(II)-mediated alterations have been reported to result in cellular death. In this regard, mangiferin has drawn attention due to its antioxidant property. The cytoprotective effect of mangiferin has been invested on $HgCl_2$-induced human liver carcinoma HepG2 cells [92]. It has shown that a 2 h pretreatment of mangiferin to $HgCl_2$ exposure at varied concentrations inhibited apoptotic cell death significantly together with a decrease in the enhanced ROS levels and reversing the activities of the antioxidant enzymes. The study suggested that the protective role of mangiferin might be due to the $HgCl_2$-induced ROS quenching, restoration of altered mitochondrial membrane potential, and intracellular antioxidant activities [77].

The universally acclaimed toxic metal, Pb, has been extensively reported to affect the endocrine, reproductive, as well as central nervous system [93]. Lead toxicity induces oxidative stress which in turn imbalances the prooxidant-antioxidant levels, affects cell membrane, interferes with transcription, disrupts the synthesis of protein, etc. [77, 93, 94]. Pb(II) interferes with –SH groups of biomolecules, calcium homeostasis, and lipid peroxidation through ROS production [95, 96]. Pal et al. have reported the ameliorative effect of mangiferin in Pb-induced hepatotoxicity [76].

Following $Pb(NO_3)_2$-induced hepatic dysfunction, posttreatment with mangiferin reduced increased ROS production; repaired the altered antioxidant machineries, viz., levels of SOD, CAT, GSH, etc.; and restored the altered mitochondrial membrane potential. The molecule significantly restored the increased levels of serum hepatic markers, viz., alanine aminotransferase and alkaline phosphatase. Mangiferin effectively downregulated the altered expressions of MAPKs, phospho-ERK1/2, phospho-JNK, and phospho-p38, inhibited the translocation of NF-κB, and reduced apoptotic hepatic cell death. In vitro studies with primary hepatocytes also reflected the beneficial role of the xanthone derivative against Pb(II)-triggered cytotoxicity [76].

Diabetes mellitus, one of the most prevalent endocrine metabolic disorder, is fundamentally associated with hyperglycemia due to defects in the secretion of insulin or varying degree of endogenous insulin resistance and results in β-cell destruction or dysfunction. Hyperglycemia is associated with excessive ROS generation and attenuation of antioxidant machineries [97]. In experimental animals, streptozotocin (STZ) is an established inducer of diabetes and is reported to induce oxidative stress through free radical generation which in turn leads to diabetic

complications [98]. In regard to this, diabetic nephropathy draws special attention which is a common consequence of both type 1 and 2 diabetes and is characterized by increased secretion of urinary albumin, mesangial thickness, thickness of basement membrane, glomerular hypertrophy and hyperfiltration, and extracellular matrix protein accumulation [77, 99]. In diabetic nephropathy, the plausible cause of ROS generation is due to the activation of advanced glycation end products, polyol pathways, increased activity of xanthine oxidase and nitric oxide synthase, glucose autoxidation, and deficiency in the mitochondrial respiratory chain [100]. In this regard, mangiferin attracts attention in the context of diabetic complications due to its antioxidant and hypoglycemic effects [101]. However, post-treatment with mangiferin on STZ-triggered diabetic rats reduced the altered antioxidant levels in both renal and cardiac tissue, reduced lipid peroxidation and glycosylation of hemoglobin, lowered the creatine phosphokinase level, and restored the STZ-induced altered levels of triglycerides, high- and low-density lipoprotein, cholesterol. Studies suggested that this antidiabetic property of mangiferin could be due to alternate mechanisms apart from insulin release and/or secretion from pancreatic β-cell [102]. Enhancement of peripheral glucose utilization, stimulation of glycogenic and glycolytic processes, and reduction of glycemia through glucose intake/uptake could be the contributing factors for the extrapancreatic actions [103]. Another study showed that treatment with mangiferin inhibits α-glucosidases [104]. Significant reduction in total cholesterol, low-density lipoprotein cholesterol, and total triglycerides with concomitant increase in high-density lipoprotein cholesterol reflected the antiatherogenic and antihyperlipidemic properties of mangiferin in diabetic animals. Mangiferin has been reported to improve oral glucose tolerance without interfering with the basal plasma glucose levels [102]. Sellamuthu et al. have reported that in diabetic rats, oral administration of mangiferin for a month reduced blood glucose levels and glycosylation of hemoglobin, whereas, the levels of hemoglobin and insulin were increased [105]. The activities of pyruvate kinase, hexokinase, glucose-6-phosphate dehydrogenase, and glycogen synthase significantly increased in diabetic rats following mangiferin administration. On the other hand, the molecule significantly reduced the altered activities of glucose-6-phosphate, lactate dehydrogenase, glycogen phosphorylase, and fructose-1,6-diphosphate in the hepatic tissue of diabetic animals, thus suggesting the antihyperglycemic effect of the molecule. Miura et al. reported that in KK-Ay mice, mangiferin diminished the increased glucose level almost by 56% and decreased the levels of triglycerides almost by 70% and blood cholesterol almost by 40% [89]. Thus findings from several studies suggested the antihyperlipidemic, antidiabetic, antihyperglycemic, and antiatherogenic properties of mangiferin in regard to diabetes and/or its associated complications.

10.6 Myricetin

Myricetin is a member of the tree families likes Myricaceae, Polygonaceae, Anacardiaceae, Primulaceae, and Pinaceae and is commonly found in vegetables, berries, wines, and teas [106, 107]. This plant-derived phenolic compound occurs both in glycosidically bound and free forms. It is used in beverages and food and exhibits diversified properties such as anti-inflammatory, antioxidant, antidiabetic, anticancer, iron-chelating activities, etc. In several diseases related to central nervous system, viz., Alzheimer's and Parkinson's, this molecule has been found to provide protection. As preservative, myricetin has been found to increase the shelf life of oil- and fat-containing food. Its interference with RNA polymerases, DNA polymerases, telomerase, kinases, transcriptase, and helicases has been reported [107].

Extensive studies suggested the antioxidant property of myricetin. In regard to the scavenging activity of the molecule, it inhibited DPPH radical significantly by 71.5% when used at a concentration of 1 mg/ml [108], whereas at a concentration of 40 g/ml, 3.2 g/ml, 32 g/ml, and 320 g/ml, the inhibition was found to be 78%, 85.6%, 92.8%, and 96.9%, respectively [109]. The inhibition of DPPH radicals by myricetin has been reported to be polyphenol oxidase mediated [110]. At 0.32 g/ml, 3.2 g/ml, and 32 g/ml, myricetin scavenged superoxide radicals by 24.6%, 79.5%, and 96.4%, respectively [111]. Significant inhibition has also been reported in respect to TEAC activity and FRAP assay [112]. The molecule, at a varied concentration significantly reduced both ascorbic acid- and ferrous sulfate-mediated peroxidation of lipid, inhibited oleic acid triggered over accumulation of triglyceride in HepG2 cells, and decreased the production of NP in the liver, brain cortex, lungs, kidney, and blood in experimental rats, exhibited NO-scavenging activity, reduced collagenase in dermal fibroblasts in human, and inhibited peroxyl radical generation [113–115, 119]. Myricetin was found to inhibit thiyl radical which acts as a catalyst during cis-trans fatty acid isomerization. In addition, the molecule was able to scavenge hydroxyl radicals which were generated through UV photolysis of hydrogen peroxide [116]. It was observed to regulate the activities and expressions of antioxidant enzymes and ROS production and hence ameliorate H_2O_2-mediated cellular death by regulating MAPK and PI3K/Akt signaling pathways [116, 117], prevented H_2O_2-triggered breakage of DNA strand in human lymphocytes and colonocytes [118], inhibited lipid peroxidation [107], and stimulated DNA repair following Fe(III)-triggered genotoxicity. Morel et al. suggested that formation of phenoxy radical could be the mode of protective action of myricetin against Fe-induced lipid peroxidation in rat hepatocytes [106], whereas another study revealed the SIN-1-mediated DNA strand breakage inhibition [108] which in turn inhibited NO and O^{2-} generation. In case of sickle cell anemia, myricetin provided protection against the red blood cells [109]. In phenazine methosulfate and xanthine oxidase system, the molecule could significantly combat against increased superoxide anions generation [110, 111]. Other probable mechanisms of myricetin'santioxidant response are mediated through altered Nrf2 activity, increased glutathione level, decreased

malondialdehyde production, and decreased leakage of lactate dehydrogenase [112]. At a lower concentration, myricetin was found to be an inhibitor of Fe-mediated lipid peroxidation, whereas a higher concentration displayed peroxidant effect against the formation of hydroxyl radicals. It is worth mentioning that in presence of bleomycin (antiviral and antitumor drug), the molecule behaved as a prooxidant (at a higher concentration) whereas behaved as an antioxidant at lower concentrations [113]. In type 2 diabetes, the molecule significantly mitigated altered protein carbonylation and lipid peroxidation [114] and reduced Ca^{2+}-induced oxidative metabolism and free radical production in the rodents' brain neurons, subjected to ischemia [119]. Xie et al. reported that that the hydroxy functional group in C-41 position in myricetin is responsible for its activity against lipid peroxide radical [115]. The structure as well as activity analysis of the molecule has revealed that the free radical scavenging activity depends on the free radical variant such as the catechol moiety of B-ring was found to be responsible for scavenging of DPPH, the hydroxyl moiety present at C-41 position was observed to be associated with xanthine oxidase generated reduction, whereas the presence of double bond at C-2-C-3 position, 3-hydroxy groups, and catechol in B-ring was found to be an attributing factor for the reducing property of myricetin [111, 116, 117].

Myricetin has been reported to be cytotoxic toward skin, hepatic, colon, and pancreatic cancer cells and plays a key role in the initiation as well as progression of cancer. The hydroxyl group of B-ring, C-2-C-3 double bond, and aromatic B-ring at C-2 has been reported to be responsible for the cytotoxic effect of the molecule. The antiproliferative activity was found against human acute leukemia cells on one hand, while the cytotoxic effect was observed in chronic leukemia cells as well as in normal peripheral blood mononuclear cells [118]. Myricetin displayed a dose-dependent effect both in vitro and in vivo in producing topo-triggered chemotherapeutics and carcinogenic effects [120]. In this context, it has been suggested that the inhibition of topo I and II was due to carbonyl moiety at C-4; hydroxyl substitution at C-3, C-7, C-31, C-41, and C-2-C-3 saturation; and hydroxyl group in B-ring [131]. Through regulation of JAK1, MEK, MKK4, and Akt kinase activity, myricetin was found to provide protection against skin cancer [122] and attenuated the induction of activator protein-1 or c-Fos activation by tumor promoter [122]. In EGF-triggered mouse JB6 P+ cells, the molecule inhibited JAK1/STAT3 signaling pathway which in turn blocked the transformation of cells and also inhibited both the transcriptional activity and DNA binding as well as phosphorylation of STAT3 at Ser727 and Tyr705 [123]. Ichimatsu et al. reported that myricetin blocked the EGF-mediated mouse epidermal cell transformation which in turn suppressed activator protein-1 [124]. Xu et al. showed a strong dose-dependent inhibitory activity of myricetin against human prostate cancer PC-3 cells and synergistically decreased cell proliferation resulted in apoptosis [125]. In bladder cancer T24 cells, the molecule significantly decreased the viability and proliferation along with the migration of the cells by reducing the expression of MMP-9 [126]. Moreover, the molecule triggered cell cycle arrest at G2/M phase, induced apoptosis by decreasing cyclin-dependent kinase cdc2 and cyclin B1 expression, and inhibited Akt phosphorylation

whereas increased p38 MAPK phosphorylation. In HepG2 cells, myricetin decreased the cancer cell proliferation, arrested G2/M phase, increased p21/p53 signaling cascade, and decreased cyclin B1 and cdc2 expression [127]. In esophageal adenocarcinoma cells, this molecule upregulated Tyr15/Thr14 phosphorylated p27 and cdc2, downregulated CDK7 kinase and CDK7 kinase-induced cdc2 phosphorylation, and induced apoptosis ([111],). It also arrested G2/M cell cycle via GADD upregulation and cyclin B1 downregulation[128, 129]. Myricetin is effectively protected against medulloblastoma by inhibiting HGF/Met pathway and prevented actin-rich membrane ruffles formation [130]. The molecule was found to be effective in causing metastasis of human lung carcinoma cells by interfering with the invasion, migration, and adhesion of cancer cells and inhibited MMP-2, phosphorylation of ERK1/2, NF-κB activation, c-Jun, and c-Fos. Myricetin induced cellular death via apoptosis and decreased the activity of PI3K in pancreatic cancer cells [130, 131]. An in vivo study showed that the molecule was potent enough to reduce the orthopic pancreatic tumor metastatic spread and tumor regression whereas was nontoxic toward untreated healthy cells. In regard to prostate cancer, the molecule served as a potent chemotherapeutic agent, whereas in colon cancer, it induced DNA condensation and cytotoxicity [132]. The compound stimulated apoptotic-inducing factor release from mitochondria and pro-carcinogen 2-amino-1-methyl-6-phenylimidazo basolateral uptake through MRP2-induced excretion of the former to the lumen from intestinal cells [133].

In vivo studies have revealed that deoxycorticosterone acetate-induced oxidative stress and hypertension were reduced following treatment with myricetin in the cardiac tissue of rats [134]. The molecule effectively reversed the otherwise altered vascular reactivity, systolic blood pressure, heart rate, levels and/or content of intracellular antioxidant enzymes, and thiobarbituric acid-reactive substances. Godse et al. showed that myricetin significantly decreased catecholamine-induced vascular reactivity and systolic blood pressure, whereas, in case of fructose rich diet, the molecule effectively lowered the blood pressure and reversed the sugar-induced altered metabolic pathway [135].

Research conducted both in vitro and in vivo confirmed the immunomodulatory role of myricetin by modulating the responses toward the immune system through antibody formation or inhibition of WBC activity. The molecule modulated LPS-triggered bone marrow-derived dendritic cells activation in mice on the one hand while on the other decreased TNF, IL-12, and IL-6 secretion along with the inhibition of cell proliferation, MHC class II, CD86, and CD40 and blockage of migratory and endocytic capacity of the cells [136]. Kang et al. elucidated the probable mode of this action of the molecule through inhibiting IL-12 production in macrophages by NF-κB downregulation [136]. The molecule stimulated cytosolic free calcium production in cultured endothelial cells of bovine and endothelium-mediated contractile responses in aortic rings of rats [137]. The molecule exhibited immunosuppressive effect by suppressing the secretion and expression of IL-2 as well as blocked CD69 expression of CD3+ T cell and mouse lymphocytes proliferation and thus reflecting its immunomodulatory activity [138].

In insulin-independent diabetes, myricetin showed protection by enhancing the glucose uptake which is independent of insulin receptors [139]. The molecule was also found to stimulate the uptake of D-3-O-methylglucose and D-glucose in the adipocyte tissue of rats. Intraperitoneal myricetin administration to streptozotocin-induced diabetic rat decreased hyperglycemia significantly whereas increased hepatic glucose-6-phosphate and glycogen content. The antidiabetic activity of the molecule was related to glycogen metabolism [140]. Islet amyloid polypeptide (IAPP) aggregation which leads to pancreatic β cell death in case of type II diabetes was inhibited by myricetin by preventing thioflavin T binding and formation of fiber [141]. Plasma glucose level was decreased, whereas insulin resistance was increased through β-endotrophin production in insulin-resistant and fructose-induced experimental animals following myricetin uptake. The molecule significantly restored the altered expression and hence functions of insulin receptor phosphorylation, insulin receptor substrate-1, Akt, and its substrate together with the translocation of glucose transporter subtype 4 [142]. Another study showed that myricetin reduced the sensitivity of insulin by regulating post-receptor signaling of insulin, GLUT-4 activity, and IRS-1-associated PI3K and decreased both the glucose-insulin index and plasma glucose concentration in the muscles of experimental animals [143]. It was observed that in the skeletal muscle cells, under hyperinsulinemic state, the molecule improved low-dose insulin-triggered uptake of glucose [111]. Myricetin displayed cytoprotection against cytokine-mediated cellular death in insulin-secreting cells, increased the viability of cells, whereas decreased cellular apoptosis, reduced cytokine-induced increased NF-κB expression, triggered accumulation of NO, stimulated ROS generation, and increased the release of cytochrome *c* in to cytosol from mitochondria. The molecule showed protection against diabetic nephropathy by reducing glomerulosclerosis, urine volume, protein excretion, and blood urea nitrogen. The altered levels of glutathione peroxidase and xanthine oxidase in the renal tissues were restored following the administration of myricetin in diabetic rats [144]. The molecule stimulated the biosynthesis of cholesterol in the hepatocytes of rats at a lower concentration whereas inhibited the biosynthesis of cholesterol at a higher concentration in HepG2 cells [145]. Chang et al. showed that myricetin decreased intracellular triglyceride accumulation in high-fat diet-fed rats, reduced body weight, and decreased visceral fat pad weights and the levels of plasma lipid [146].

10.7 Conclusion

Extensive studies reveal the pharmacological activities of the phytochemicals. There is no doubt that phytochemicals hold a potential in protecting against several diseases and/or pathophysiological conditions. These molecules may work either through synergistic interaction or when administered unaccompanied. However, regardless of the studies (both in vivo and in vitro) which have elucidated on the role of phytochemicals related to human health, further extensive research is required to understand the specific molecular mechanism of the phytochemicals. Detailed

preclinical studies and its clinical experiments are needed to provide a basis for potential expediency of these gifts of nature in the welfare of human health.

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