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Herbal Medicines and Nutraceuticals for Diabetic Vascular Complications: Mechanisms of Action and Bioactive Phytochemicals

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Abstract: Diabetes is one of the most prevalent chronic diseases throughout the world. The majority of its complications arise from vascular-related inflammation apparently initiated by endothelial cell injury. One cause of this injury has been attributed to hyperglycaemia-induced reactive oxygen species. Consequently, current drug developmental strategy has targeted specific inflammatory and oxidative stress pathways for the prevention of diabetic vascular complications. Herbal medicines have traditionally been used for the treatment of diabetes and its complications. In fact, current pre-clinical and clinical studies have demonstrated that many of them exhibit potent anti-inflammatory and anti-oxidative properties, and have also identified the active phytochemicals responsible for their activities. The present review summarises the latest research on the molecular mechanisms of diabetic vascular complications, and evaluates the level of scientific evidence for common herbal medicines and their bioactive phytochemicals. These agents have been shown to be effective through various mechanisms, particularly the NF-κB signalling pathways. Overall, herbal medicines and nutraceuticals, as well as their bioactive components, which exhibit anti-inflammatory and anti-oxidative properties, provide a promising approach for the prevention and treatment of diabetic complications.

Keywords: Anti-oxidants, diabetic complications, herbal medicines, inflammation, mechanisms of action, nutraceuticals, phytochemicals.

1. INTRODUCTION

The incidence of diabetes is escalating globally. The prevalence of diabetes amongst all age-groups worldwide is estimated to increase from 2.8% in 2000 to 4.4% in 2030 [1]. This correlates to the total number of people with diabetes rising from 171 million in 2000 to a staggering 366 million in 2030 [1, 2]. Comparing the different types of diabetes, Type 2 diabetes is responsible for 90 to 95% of diabetes cases which are a direct result of increased urbanization, high rates of obesity, sedentary lifestyles and stress. Not only does diabetes negatively impact the health and social well-being of sufferers, it also brings forth devastating economic impact. It is expected to overwhelm global healthcare services, wipe out some indigenous populations and undermine economies, especially in developing countries. As for countries in Asia, the Middle East, Oceania and the Caribbean, diabetes affects up to 20% of the adult population and, in fact, these countries bear substantial health and economic impacts as a consequence of this diabetes prevalence [3].

Diabetes is a chronic disease that occurs when the pancreas does not produce sufficient insulin, or when the body is unable to efficiently utilize the produced insulin. It is characterized by chronic hyperglycaemia, or raised blood glucose level, commonly present in chronic, uncontrolled diabetes. Over time, this results in serious damage to many body systems, including the blood vasculatures. Many molecular studies have demonstrated that hyperglycaemia induces vascular inflammation by initiating endothelial cell injury through various inter-related mediators, one of which is attributed to hyperglycaemia-induced reactive oxygen species (ROS) [4, 5]. Pathological changes in the diabetic vasculature can alter organ perfusion, particularly affecting organs which are heavily dependent on their microvascular supply, such as the retina, kidneys and peripheral nervous system; and those dependent on macrovascular supply, including the heart, brain and limbs. Microvascular disease may also contribute to peripheral vascular disease, reduced myocardium vascularization and compromised wound healing processes [6].

Managing diabetic vascular complications has been a continuous challenge for many decades. To some extent, diabetic vascular complications have been overlooked in terms of their clinical impact and complex anti-inflammatory and anti-oxidative pathways. Nevertheless, there are increased pre-clinical, as well as clinical evidence, to demonstrate the potential of herbal medicines and nutraceuticals in targeting diabetic complications. In this review, we will focus on the clinical and biological activities of herbal medicines and nutraceuticals and identify the bioactive phytochemicals and their respective molecular mechanism(s) of action(s) in diabetic complications.

1.1. Diabetic Complications: Issues and Challenges

Diabetes is a serious disease with detrimental health complications and premature mortality. The disease is also a result of the many detrimental metabolic changes, collectively known as metabolic syndrome or syndrome X. Diabetes contributes to over 10% of total health care expenditure in many countries. Globally and across all ages, it is estimated that at least 1 in 20 deaths are attributable to diabetes and its complications. In adults aged 35 to 64, the proportion increases dramatically; at least 1 in 10 deaths [2]. However, statistics may underestimate the actual mortality from diabetes [7]. This is because individuals with diabetes most often die from cardiovascular and renal-related complications, and not from a cause directly related to diabetes, such as ketoacidosis or hypoglycaemia [8].

Elevated blood glucose level is a common result of uncontrolled diabetes and, over time, can damage the heart, eyes, kidneys and nerves, mainly through deteriorating blood vessels supplying the organs. Some health complications from diabetes include diabetic retinopathy, a significant cause of blindness which occurs as a result of long term damage to the small blood vessels in the retina. After 15 years of diabetes, around 10% of patients may develop

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severe visual impairment. Another complication affecting up to 50% of diabetic sufferers is diabetic neuropathy which constitutes damage to the nerves and the microvessels supplying the nerves' tissue. Common symptoms are tingling, pain, numbness, or weakness in the feet and hands. Combined with reduced blood flow, neuropathy in the foot increases the onset of foot ulcers and eventual limb amputation. Moreover, diabetes is among the leading causes of kidney failure and approximately 10-20% of people with diabetes succumb to kidney failure. Diabetes also increases the risk of heart disease and stroke, with a 50% mortality rate of cardiovascular disease [9].

The pathologic imprint of diabetes and hyperglycaemia often involves the vasculature, where the primary source of its damaging consequences begins. Given that stroke and acute coronary syndromes are the common complications resulting from diabetes, much attention has focussed on the prevention of diabetic macrovascular diseases. Indeed, the morbidity associated with diabetic microvascular complications, including retinopathy, neuropathy, nephropathy, and limb ischemia is also an important issue when considering the patients' quality of life [9]. With the impact of diabetic vascular disease, phenomenal effort has been directed to improve vascular outcomes, particularly in Type 2 diabetes. Improving macrovascular outcomes through glucose-lowering interventions has remained a largely ineffective endeavour. Nevertheless, strict glucose control does minimize microvascular complications in diabetes [4]. This vascular mechanism appears somewhat contradictory and requires re-evaluation of the diabetic vascular disease therapeutic spectrum. It is conclusive that many of the complications are initiated by vascular inflammation as a result of chronic exposure to hyperglycaemia [4, 5]. Therefore, many studies have focussed on identifying specific vascular anti-inflammatory and anti-oxidative agents to prevent diabetic vascular complications.

1.2. Current Treatments for Diabetes and Vascular Complications

The initial approach in diabetes management is lifestyle modifications. Before administrating medication, a healthy dietary pattern and physical activity program is the mainstay of diabetes treatment. When lifestyle modification fails, diabetic medications become a necessity. The basic theory of clinical medications for diabetes aims to control and restore glucose homoeostasis in both the postprandial and fasting state. This can be achieved through different mechanisms, such as reducing glucose absorption and hepatic glucose output, as well as enhancing pancreatic insulin secretion, insulin sensitivity and peripheral glucose utilization. Based on these mechanisms, medications are categorized into insulin, sulfonylurea, thiazolidinediones, biguanides, alpha-glucosidase inhibitors, insulin-like growth factor, and incretin mimetics and enhancers [10, 11].

Studies have shown that, with good management, many diabetic complications can be prevented or delayed [12, 13]. Medication often plays the important role of controlling blood glucose and lipid levels in diabetes. However, managing diabetic vascular complications *via* this mechanism has been perplexing, and is not guaranteed to be successful [14]. Therefore, an agent which is capable of directly regulating vascular homeostasis, thus preventing vascular injury and inflammation, would be the best therapeutic option for diabetic vascular complications. Currently, there are few ongoing clinical trials targeting different key pathways and transcription factors associated with diabetic vascular damage, involving drugs such as aminoguanidine, alagebrium, benfotiamine and ruboxistaurin [5]. Another area which will contribute towards drug discovery strategy against diabetic vascular complications is in herbal medicines and nutraceuticals, which is the central theme of this review.

2. MECHANISMS FOR DIABETIC VASCULAR COMPLICATIONS

2.1. The Involvement of Vascular Inflammation in Diabetic Complications

Ethical issues are raised when clinical trials are conducted without supporting *in vitro* evidences on herbal medicines and nutraceuticals. In current research trends, animal studies and cellular studies generate valuable preliminary information in the potential efficacy and molecular mechanisms of herbal medicines for clinical trials. However, the selection of suitable herbal medicines for evaluation is based on reverse pharmacology. Simply put, the particular herbal preparation under evaluation is selected in accordance with traditional records and observational documentations. Based on these records, we can select particular molecular pathways underlying the actual mechanism of action of the herbal medicine for a particular condition. Sufficient understanding about the disease condition is vital for deciding which molecular pathways are investigated.

Studies have demonstrated that inflammation is one of the main contributing factors in both atherosclerosis and Type 2 diabetes [15, 16]. Hyperglycaemia can promote vascular complications through multiple inter-related pathways and mechanisms. According to Hamik *et al.* (2005), at least four major molecular pathways have been attributed in the development of diabetic vascular complications. They include oxidative stress, protein kinase C (PKC), polyol/aldose reductase and advanced glycation end product (AGE)–receptor of AGE (RAGE) pathways. In addition, nuclear transcription factors such as activated protein-1 (AP-1), mitogen-activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB) play a significant role in promoting diabetic vascular complications [4, 5]. The molecular mechanisms of diabetic vascular inflammation, including associated intermediate effects and consequences, are summarized in Table **1**.

2.2. Molecular Mechanisms Involved in NF-κB Signalling Pathway

This review will focus primarily on NF-κB mediated inflammatory response, such as leukocyte recruitment which is a crucial feature in atherosclerosis and diabetic complications, and the molecular mechanisms involved [17-19]. NF-κB is a major and central heterodimeric transcription factor involved in the regulation of inflammatory responses of many cell types. NF-κB activation triggers the production of pro-inflammatory cytokines, adhesion molecules, chemokines, inflammation-related enzymes and other factors, which are important inflammatory markers for many chronic inflammatory conditions, including atherosclerosis [20]. Several steps govern the molecular mechanisms involved in NF-κB signalling. NF-κB usually exists in a latent form in the cytoplasm of unstimulated cells coupled with an inhibitor protein, IκB, with the mammalian form of IκB named as IκBα [21]. Upon stimulations with inflammatory cytokines (e.g. TNF-α, IL-1β and IL-6), high glucose level and oxidative stress, these lead to the activation of NF-κB, mainly characterized by its p50/p65 dimeric subunit and its association with IκBα. These stimuli trigger the activation of the IκB kinase (IKK) complex by phosphorylation which is composed of several significant subunits e.g. IKKα, IKKβ and IKKγ. The activated IKK complex is then capable of phosphorylating IκBα and releasing the NF-κB p50/p65 dimeric subunit, the predominant form of activated NF-κB in many cell types [21]. This results in its translocation to the nucleus. As a consequence, the dimer binds to the target gene region and stimulates the transcription of the target gene, which participates in the inflammatory responses, especially in endothelial cells (Fig. **1**).

Table 1. Summary of the Molecular Signalling Pathways and Mechanisms Implicated in the Development of Diabetic Vascular Inflammation; and Some Suggestions on the Potential Therapeutic Strategies in Relation to the Prevention of Diabetic Vascular Complications [4, 5]

Pathway	Mechanisms	Intermediate Effects	End Results	Therapeutic Strategies
Oxidative stress	Hyperglycaemia induces production of reactive oxygen species (ROS)	Damage to cellular proteins, reduced nitric oxide level, activation of transcription factors such as AP-1 and NF-κB	Increased level of pro-inflammatory cytokines e.g. TNF-α, IL-6, and IL-1β, and mediators e.g. intercellular adhesion molecule-1 (ICAM-1), which confer a pro-adhesive and pro-thrombotic properties to the endothelial cells	Anti-oxidative, anti-inflammatory agents
Protein kinase C (PKC)	Hyperglycaemia-induced diacylglycerol directly activates PKC; ROS and AGE-RAGE pathways indirectly activate PKC	Influence production of endothelial nitric oxide synthase (eNOS) and endothelin; increase ROS production; induce adhesion molecule expression e.g. vascular cell adhesion molecule-1 (VCAM-1); pro-fibrotic factors e.g. transforming growth factor b1 (TGFb1) and connective tissue growth factor (CTGF)	Disturbance on the balance of vasodilatory/ vasoconstrictive activities, and possess pro-adhesive and pro-thrombotic properties of the vessel walls	Selective PKC (b subtype) inhibitors
Polyol/aldose reductase	Activation of the hyperglycaemia-induced aldose reductase enzyme, which converts glucose to sorbitol and ultimately to fructose	Nicotinamide adenine dinucleotide phosphate ($NADPH/NADP^+$) oxidase balance is disturbed that leads to intensification of oxidative stress pathway	Enhance the end results of oxidative stress pathway, thus stimulate production of more pro-inflammatory cytokines and mediators as well as pro-thrombotic factors	Aldose reductase inhibitors, anti-oxidative, anti-inflammatory agents
Advanced glycation end products-receptor of AGE (AGE-RAGE) pathway	Chronic hyperglycaemia, in addition to oxidative stress and inflammatory conditions, induce irreversible glycation of proteins and lipids	These products may cross link with the long-lived proteins such as collagen or elastin and other inter-molecular factors in the vessel wall; and binding of AGE to its receptor (AGE-RAGE effects) on vascular cells can activate multiple inflammatory signalling pathways and factors including monocyte chemoattractant protein-1 (MCP-1)	Changes in structural integrity and elasticity of the vessel wall, enhance production of ROS and other pro-inflammatory cytokines as well as recruitment of leukocytes to inflammatory sites within the vessels, and upregulation of RAGE itself	Inhibitors of AGE and RAGE activation, anti-inflammatory, anti-oxidative agents, and protein cross linking inhibitors
Nuclear transcription factors pathways	Activation of NF-κB, AP-1, and MAPK transcription factors via oxidative stress, PKC and AGEs pathways induced by hyperglycaemia	Translocation of transcription factors into the nucleus	Activation of translational activities on pro-inflammatory related genes, thus promoting expression of inflammatory cytokines	Selective nuclear factor inhibitors
Renin-angiotensin activation pathway	High glucose activates matrix-degrading metalloproteinases, and vascular smooth muscle cells (VSMC) remodelling	VSMC proliferation, migration and altered reactivity	Plaque rupture, arterial remodelling i.e. loss of elasticity and acquire stiffness	Inhibitors of renin-angiotensin system

2.3. The Relationship between Anti-oxidative and Vascular Inflammatory Properties

A crucial feature in diabetic vascular complications is vascular inflammation which is characterized by the presence of leukocyte recruitment which is mostly initiated by adhesion molecules and chemokines, inflammation-related enzyme production (e.g. inducible nitric oxide synthase (iNOS)) and pro-inflammatory cytokine production (e.g. TNF-α, IL-1β and IL-6) (Fig. **2**). Many research studies have been conducted to elucidate the mechanistic correlation of anti-oxidant and anti-inflammatory properties of synthetic agents. Cominacini *et al.* (1999) showed that troglitazone, a thiazolidionedione compound with anti-oxidative activities, prevented NF-κB-mediated adhesion molecule expression of endothelial cells [22, 23]. However, pioglitazone (another thiazolidionedione compound without anti-oxidant activity) was capable of increasing peroxisome proliferator-activated receptors (PPAR) -γ activity but failed to suppress NF-κB activation [22, 24]. Therefore, a potential

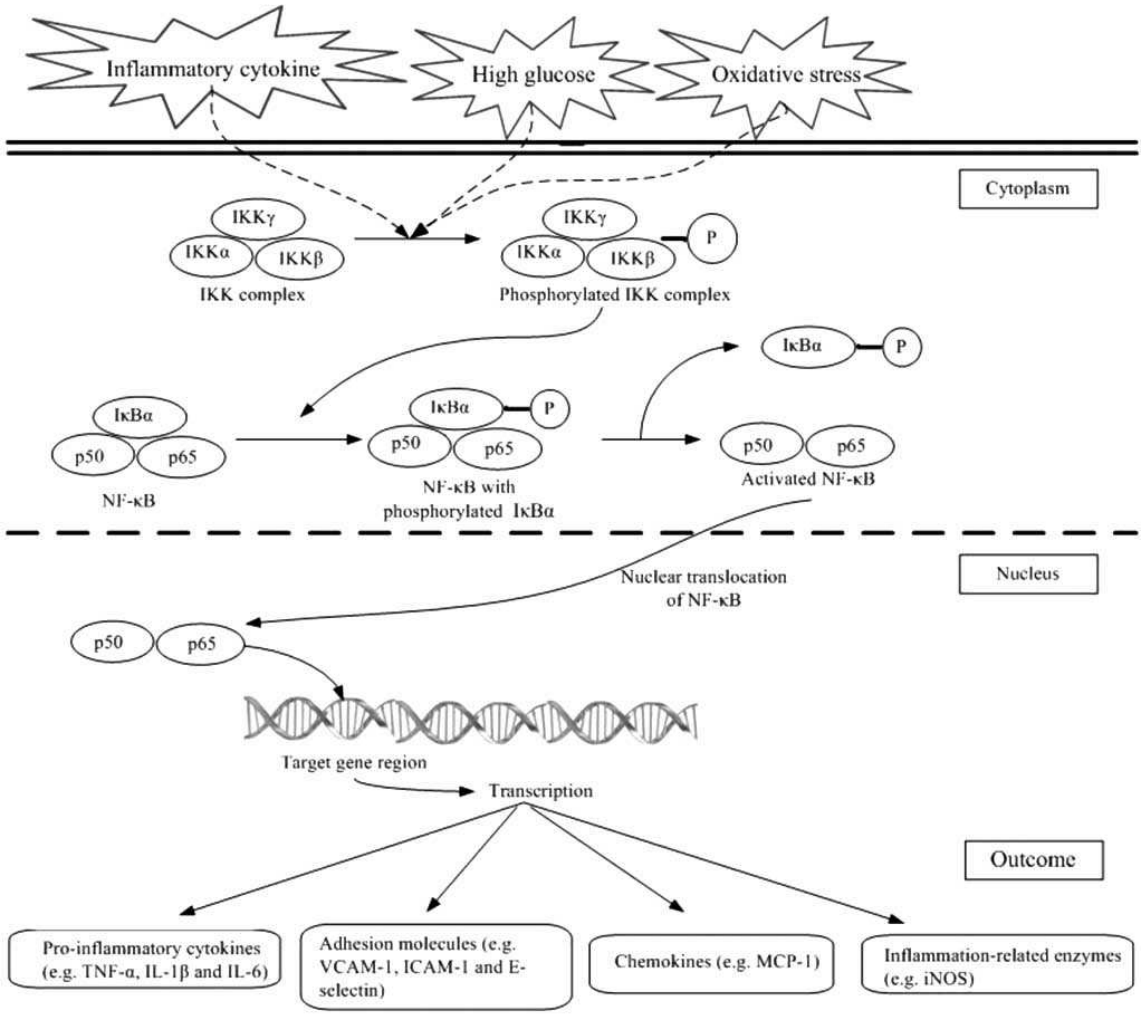


Fig. (1). Schematic diagram of NF-κB signalling pathway in relation to inflammation.

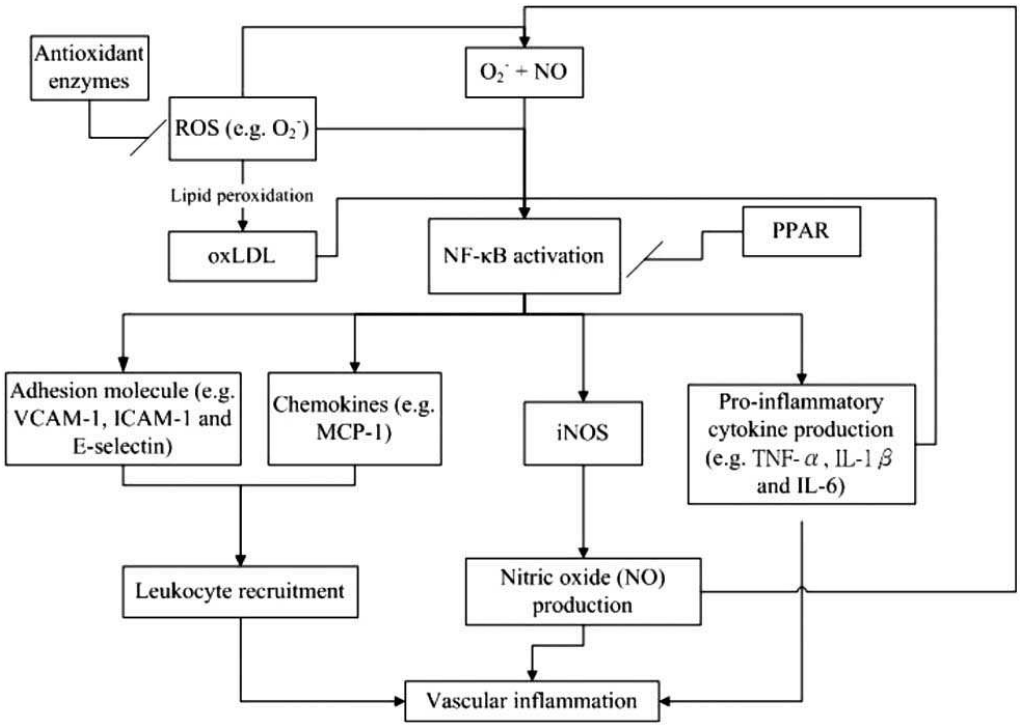


Fig. (2). Schematic diagram of pathways involved in vascular inflammation.

linkage between a compound's anti-oxidative and anti-inflammatory activities by modulating NF-κB activities would be beneficial. One proposed mechanism for the inhibitory effects of anti-oxidants on vascular inflammation involves the role of cellular ROS in the mediation of NF-κB activation (Fig. **2**). It has been suggested that the increase in oxidative stress i.e. the increase in intracellular ROS such as hydrogen peroxide (H_2O_2), superoxide (O_2^-) or hydroxyl radical (•OH), can stimulate the activation of NF-κB [21]. For example, the interaction between O_2^- and nitric oxide (NO) forms the reactive peroxynitrite ($ONOO^-$) [25]. This, in turn, stimulates the NF-κB-mediated gene expressions of pro-inflammatory cytokines (e.g. TNF-α) adhesion molecules (e.g. VCAM-1, ICAM-1 and E-selectin), chemokines (e.g. MCP-1) and inducible enzymes (e.g. iNOS) [26]. This hypothesis was supported by several studies such as the addition of H_2O_2 activated NF-κB in cellular assays [27]. Also, pro-inflammatory cytokines (e.g. TNF-α, IL-1β and IL-6) stimulated the release of intracellular O_2^- in endothelial cells, and, in turn, activated NF-κB [27]. Pyrrolidine dithiocarbamate, a radical scavenging anti-oxidant, is used as a metal chelator to prevent TNF-α-stimulated NF-κB activation. It has also been shown to reduce VCAM-1 expressions and monocyte adhesion which are mediated by NF-κB activation [27]. In addition, pyrrolidine dithiocarbamate inhibited NF-κB-regulated iNOS expression [28]. Overall, scientific evidence demonstrate that oxidative stress and NF-κB activation are closely related, and therefore anti-oxidants are potentially important modulators of vascular inflammation, as well as diabetic vascular complications.

3. HERBAL MEDICINES AND NUTRACEUTICALS FOR DIABETES

3.1. Efficacy, Safety and Quality of Herbal Medicines

Studies have demonstrated the potential health benefits of herbal medicines and nutraceuticals in diabetes and its vascular complications (e.g. atherosclerosis). In addition to dietary and lifestyle modifications, herbal medicines and nutraceuticals may offer extra health benefits for the management of diabetes and diabetic vascular complications.

Multi-target, multi-channel and synergistic properties are the common features in the actions of herbal medicines and nutraceuticals, due to the variety of constituents within a single natural product. Owing to these properties, herbal medicines and nutraceuticals may be beneficial in dealing with diabetes itself, as well as its complications, due to the fact that various mechanisms are involved in diabetic vascular complications. Over centuries, herbal medicines in traditional Chinese, Ayurvedic and Unani medical practices have played an important role clinically for different disease states based on traditional and clinical records. As many prescription medicines have narrow therapeutic windows and possess unwanted side effects, herbal medicines and nutraceuticals provide a valuable resource of effective and safe therapeutic agents. This has resulted in a commercially significant market and rise in international attention, recognition and usage of herbal medicines. Accordingly, the efficacy, safety and quality of herbal medicines have become major issues, as most reported therapeutic effects are based on practitioners' experience and traditional records. Many natural products are sold without prescription and consist of a decoction of several herbal materials defined in a formula. In most cases, their exact efficacy and mechanism of action have not been rigorously examined in a scientific setting. Also, the pharmaceutical approach of analysing a single component cannot be applied in discerning the quality of a natural preparation. Thus, quality control methods which reflect the holistic approach of complementary medicine have to be developed in order to determine the chemical basis of herbal medicines and nutraceuticals [29].

Thus, we have proposed multiple chromatographic methods as a comprehensive platform for the quality evaluation of herbal medicines. The methods include pharmacognostic and DNA fingerprinting and quantitative thin layer chromatography (TLC), high pressure liquid chromatography (HPLC), capillary electrophoresis (CE) and carbohydrate determination. The analysis will generate information on the various types of phytochemical components contained within the herbs and provide chemical, bioactive and toxic markers. To compare the large amount of data derived from samples or products, statistical analysis *via* chemometrics is used to generate patterns, or groups. If the analysis is correlated with biological activity or clinical studies, then a new standard can be set [30, 31].

Natural products often have a complex phytochemical composition and there is also a lack of information regarding their toxicity profile. Traditional documentation has strict guidelines on the type, location and preparation of herbs to avoid noxious effects. Novel sources of information and the use of more recent toxicological assessment techniques such as predictive toxicology and toxicomics can help to reduce the uncertainty in decision making with respect to the natural product [32]. The activities of herbal medicines are aimed at the systemic level *via* interactions with a multitude of targets in the human body. The idea of the whole herb or multi-herb preparation not only addresses multiple targets, but may also cancel out the toxicity and side-effects of a single, isolated compound from the plant. The formulation principle of multi-herb intervention strategy is a systemic approach for the treatment and prevention of disease [33], unlike prescription medicine which may only target one pathway of the disease and instigate side-effects in another.

3.2. The Level of Scientific Evidence of Herbal Medicines

The body of scientific information on herbal medicines and nutraceuticals covers preclinical and clinical studies. Many systems are available to evaluate the level of evidence and the impact of clinical studies including the methods used by the Australian National Health and Medical Research Council (NHMRC) and the Therapeutic Goods Administration (TGA). The TGA system categorizes clinical evidence into "High", "Medium", "General", and "Supporting Evidence" [34, 35].

"High" level is for evidence obtained from a systematic review of all relevant randomised controlled trials, without significant variations in the directions or degrees of results (equal to NHMRC level I), or evidence obtained from at least one properly designed randomised controlled (preferably multi-centre) double blind trial (NHMRC II). "Medium" level is for evidence obtained from well designed controlled trials without randomisation (NHMRCIII-1), or evidence obtained from well designed analytical studies, preferably from more than one centre or research group, including epidemiological cohort and case-control studies (NHMRCIII-2), or evidence obtained from multiple time series with or without intervention (NHMRCIII-3). "General" level is for descriptive studies, case series or reports of relevant expert committees (NHMRC IV). "Supporting evidence" includes non-human data from *in vitro* and animal studies, and non-clinical information from biochemical, nutritional and microbiological studies. Texts such as TGA-approved Pharmacopoeias or monographs which constitute traditional usage are included here.

The clinical evidence rankings often do not include preclinical studies which dominate herbal medicines and nutraceuticals studies. Traditional pharmacology attempts to mimic the clinical situation by generating data from whole animal activities. Cellular studies, particularly molecular and cell biology, have underlined the efficacy and mechanism of action of traditional medicines and nutraceuticals. Phytochemistry and quality analysis are a recognised foundation of efficacy and safety of herbal medicines and nutraceuticals. Therefore, to evaluate the significance of scientific data on herbal medicines and nutraceuticals, we propose that the levels of scientific evidence based on the TGA system are extended to include three clinical evidences: "High", "Medium" and "General";

and three preclinical evidences: "Animal studies", "Cellular studies", and "Chemical studies" which includes pharmaceutics, biochemical, nutritional, microbiological, phytochemical and quality analysis studies (Table **2**). This system is consistent with the concept of bioequivalence in herbal medicine, which defines that the equivalence of herbal products requires evidences from all pharmaceutical, pharmacokinetic, pharmacodynamic and therapeutic levels [31, 36].

3.3. Traditional Chinese Medicines for Diabetes

Traditional Chinese medicine is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles which differ from those of orthodox/conventional medicine or Western naturopathy. In traditional Chinese medicine, diabetes is described as "Xiao Ke", a term related to the typical symptoms of a diabetic patient: weight loss and thirst. The disease was described in the ancient traditional Chinese medicine classic book *Inner Cannon of the Yellow Emperor,* and is understood to be caused by excessive food intake, emotional trauma, weakness of Zhangfu organs. The treatment principle for this condition is clearing the Heat and nourishing Yin. There are three types of diabetes syndromes: Upper Type: heat in the lung which consumes body fluid and treated with formula for diabetes by clearing the heat; Middle Type: excessive heat in the stomach and treated with Jade Maid Decoction; and Lower Type: deficiency of kidney Yin and deficiency of Yin and Yang and treated with Six Ingredients Rehmannia Pill by nourishing Yin and strengthening the kidney [37-39].

Whilst the diagnostic techniques and differentiation of syndromes requires full traditional Chinese medicine expertise, the pharmacological studies of Chinese herbs have greatly facilitated the understanding of traditional Chinese medicine mechanism of action. The common tonifying (nourishing) herbs are *Rehmannia glutinosa, Panax ginseng, Dioscorea opposita, Lycium babarum, Polygonatum odoratum, Ganoderma lucidum, Astragalus membranaceus* and *Paeonia suffruticosa.* The pharmacological functions of this category of herbs include enhancing immune and endocrine function, regulating glucose and lipid metabolism, central nervous system, and cardiovascular activity [40-42].

The common heat-clearing herbs are *Scutellaria baicalensis, Anemarrhena asphodeloides, Coptis chinensis, Lonicera japonica, Isatis indigotica* and *Pueraria lobata.* The pharmacological functions of this category of herbs are enhancing the immune function as well as exhibiting anti-bacterial, anti-viral, anti-pyretic, sedative, anti-hypertensive, anti-inflammation, hypoglycaemia and diuretic properties [41, 42].

According to traditional Chinese medicine theory, diabetic complications may belong to various traditional Chinese medicine syndromes. For example, coronary heart disease can be treated by herbs which promote blood circulation such as *Salvia miltiorrhiza*, *Paeonia suffruticosa*, *Crataegus pinnatifida* and *Cinnamonum cassia* [43]. Guanxin II formula composed of *Salvia miltiorrhiza*, *Paeonia suffruticosa*, *Ligusticum chuangxiong, Carthamus tinctoris* and *Dalbergia odorifera*, is shown to be safe, cheap and effective in the management of coronary heart diseases. The underlying mechanism was shown to be related to its anti-ischemic, anti-apoptotic, anti-oxidative, anti-platelet and anti-inflammatory activities. Phytochemicals, including Tanshinol, hydroxysafflor yellow A and ferulic acid are believed to be responsible for the cardio-protective effect of Guanxin II [44]. Sodium ferulate or 3-methoxy-4-hydroxycinamate sodium is an active principle from *Angelica sinensis, Cimicifuga heracleifolia, Ligusticum chuangxiong*, and other plants. It has been used in traditional Chinese medicine for several decades and is approved by the State Food and Drugs Administration of China as a drug for the treatment of cardiovascular and cerebrovascular diseases and to prevent thrombosis. Sodium ferulate has antithrombotic, platelet aggregation inhibitory and anti-oxidative activities in animals and humans. Clinical results have been obtained with sodium ferulate in coronary heart disease, atherosclerosis, pulmonary heart disease and thrombosis [45].

Gynostemma pentaphyllum is a commonly consumed medicinal plant in traditional Chinese medicine which has been reported to be beneficial in the management of diabetes, atherosclerosis, inflammation and diabetic complications [46-53]. In a recent human clinical study from the Karolinska Institute, an anti-diabetic effect of *Gynostemma pentaphyllum* tea was demonstrated after a 12 week treatment, demonstrating a decrease in fasting glucose levels, glycosylated haemoglobin levels and a change in homeostasis model Assessment-insulin resistance compared to the control group [46]. A dammarane-type saponin, described as phanoside (racemic mixture) from an ethanolic extract of *Gynostemma pentaphyllum,* stimulated insulin-release 10-fold from pancreatic islet cells from Wistar rats at a concentration of 500 μM [53].

Another most widely consumed medicinal plant is tea. Many research studies have demonstrated the beneficial effects of green tea (*Camellia sinensis*) with high polyphenol content on atherosclerosis, coronary heart disease, hypertension, diabetes, metabolic syndrome and obesity, which are common features in diabetes and diabetic complications [54].

3.4. Common Herbs and Nutraceuticals for Diabetes

From literature, common herbs and nutraceuticals known to have hypoglycaemic, anti-inflammatory, anti-oxidative and lipid-

Table 2. Ranking System for the Levels of Scientific Evidence for Herbal Medicines and Nutraceuticals [34]

Ranking	Level of Scientific Evidence	Intervention and Scientific Evidence
1	High	A systematic review A randomised controlled trial
2	Medium	A pseudo-randomised controlled trial A comparative study with concurrent controls A comparative study without concurrent controls
3	General	Case series
4	Animal studies	*In vivo* studies
5	Cellular studies	*In vitro* studies
6	Chemical studies	Pharmaceutics, biochemical, nutritional, microbiological, phytochemical and quality analysis studies

lowering effects are aloe (*Aloe vera*), *Andrographis paniculata*, *Astragalus membranaceus*, baical skullcap (*Scutellaria baicalensis*), bilberry (*Vaccinium myrtillus*), bitter melon (*Momordica charantia*), cinnamon (*Cinnamomum zeylanicum*), clove (*Syzygium aromaticum*), evening primrose oil (*Oenothera biennis*), fenugreek (*Trigonella foenum graecum*), fish oil, flaxseed oil (*Linum usitatissimum*), garlic (*Allium sativum*), ginger (*Zingiber officinale*), ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), goldenseal (*Hydrastis canadensis*), grape seed (*Vitis vinifera*), green tea (*Camellia sinensis*), *Gymnema montanum*, hawthorn (*Crataegus monogyna*), honey, licorice (*Glycyrrhiza glabra*), oats (*Avena sativa*), olive (*Olea europaea*), psyllium (*Plantago ovata*), turmeric (*Curcuma longa*), wild yam (*Dioscorea opposita*), *Withania somnifera* and wolfberry (*Lycium barbarum*) [55, 56]. Other herbs with similar properties include gotu kola (*Centella asiatica*), pomegranate (*Punica granatum*) and propolis.

This paper reviews medicinal plants and nutraceuticals that have shown clinical or experimental activities to treat or prevent diabetic complications. We searched Medline, PubMed and Cochrane reviews for literature dating from 1980 to 2010 using the following keywords, "herbal medicine", "diabetic complications", "medicinal plant", "herb", "diabetic cardiovascular complications", "diabetic", "endothelial dysfunction", "diabetic nephropathy", "diabetic neuropathy", and "diabetic retinopathy". For common herbs and supplements, and important medicinal plants from traditional Chinese medicine for diabetes treatment mentioned above, a further PubMed search was performed using the name of that herb. Due to the vast number of available *in vitro* cellular studies, we have specifically focussed on the results from human and diabetic animal subjects. These medicinal plants and nutraceuticals are summarized in Table **3** [50, 57-177]. The most effective and commonly studied natural products with high levels of evidence are *Capsicum frutescens, Centella asiatica,* fish oil, *Ginkgo biloba, Linum usitatissimum, Pinus pinaster, Salvia hispanica, Salvia miltiorrhiza, Tinospora cordifolia* and *Vitis vinifera*. The natural products with only medium or general level of evidence are *Astragalus membranaceus, Cinnamomum zeylanicum, Glycine max,* honey, *Juglans regia, Panax notoginseng,* propolis and *Punica granatum.* Additionally, many different varieties of natural products have shown efficacy in treatment and prevention of diabetic complications in animal studies only, including *Allium sativum, Aloe vera, Angelica sinensis, Carica papaya, Camellia sinensis, Cinnamonum cassia, Colocassia esculenta, Curcuma longa, Dioscorea cayenensis, Eugenia jambolana/ Syzgium cumini, Ganoderma lucidum, Gymnema montanum, Gynostemma pentaphyllum, Lycium barbarum, Medicago sativa, Momordica charantia, Oenothera biennis, Olea europaea, Paeonia suffruticosa, Panax ginseng, Polygonatum odoratum, Pueraria lobata, Rehmannia glutinosa, Rheum officinale, Rhodiola rosea, Silybum marianum, Trigonella foenum graecum, Vaccinium myrtillus, Withania somnifera* and *Zingiber officinale*.

4. BIOLOGICALLY ACTIVE PHYTOCHEMICALS FOR DIABETIC COMPLICATIONS

Biologically active phytochemicals from herbal medicine and nutraceuticals contribute to their health benefits. Based on our literature search, many phytochemicals have been evaluated for their beneficial effects in diabetic complications in diabetic animal studies and clinical trials. Their activities are summarized in Table **4** [93, 178-222]. These phytochemicals were selected using the following keywords, "diabetic complication" and "herbal" or "herb", "or "natural product" or "phytochemical" or "flavonoid" with the limits "human", "animal", "English" from the PubMed database. According to our selection criteria, γ-linolenic acid was reported to have beneficial effects in diabetic complications in a double-blinded placebo-controlled trial. Many other phytochemicals were also shown to be effective in managing diabetic complications in diabetic animal models including astilbin, astragaloside IV, astragalus saponins I, baicalein, berberine, breviscapine, curcumin, delphinidin, docosahexanoic acid, epigallocatechin gallate, eugenol, genistein, isoliquiritigenin, α-lipoic acid, lithospermate B, lithospermic acid B, *Lycium barbarum* polysaccharide 4, magnolol, maltol, mangiferin, oleanolic acid, protocatechualdehyde, puerarin, quercetin, resveratrol, rhein, rutin, scoparone, scutellarin, α-spinasterol, tanshinone IIA , tetrandrine, troxerutin and vitamin E.

4.1. Phytochemicals with Anti-Oxidative and Anti-Inflammatory Properties

From the community and popular point of view, phytochemicals with significant anti-oxidant power are often expected to demonstrate considerable beneficial effects in different disease conditions such as cardiovascular disease, diabetes and inflammation. An extensive number of scientific studies have been conducted to evaluate the potential health benefits of different phytochemicals for diabetic vascular complications. Published work demonstrates that many phytochemicals from the four major categories (i.e. lipids, nitrogen containing compounds, phenolics and terpenoids) are able to modulate vascular inflammation by targeting the above mentioned inflammatory pathways. The representative phytochemicals are summarized in Table **5** [25, 47-49, 217, 223-390]. It is noted that most of these phytochemicals also possess significant anti-oxidative activities, mainly by reducing the production of ROS, preventing lipid peroxidation, modulating anti-oxidant enzyme levels (e.g. glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase and catalase) and the ability to scavenge oxidants. However, the exact structural relationship between the phytochemicals' anti-inflammatory and anti-oxidative activities is not well defined.

4.2. Phytochemicals Involved in the Inhibition of Vascular Inflammation

A considerable amount of research has been performed to clarify the molecular mechanisms of phytochemicals involved in inhibiting vascular inflammation. In this review, we have provided a summary of the phytochemicals specifically inhibiting leukocyte recruitment and NF-κB signalling pathways. In addition, their activities on other NF-κB-regulated proteins, particularly the production of iNOS and pro-inflammatory cytokines, are also included. Since PPARs down-regulate NF-κB signalling pathway, the PPAR activities of these phytochemicals are also reported [25, 47-49, 217, 223-231, 233-237, 239-241, 243, 244, 246-254, 258-269, 271-273, 276-278, 280-283, 286-294, 297-303, 305, 306, 308, 313-315, 319, 321-328, 332-347, 349-358, 361, 363-370, 372-374, 376-380, 382, 384-387, 389].

As well as for diabetic complications, NF-κB and its signalling pathways are attractive targets for the treatment of other inflammatory diseases such as asthma, cancer and autoimmune disease. This is because NF-κB is a transcription factor responsible for encoding the gene in the production of pro-inflammatory cytokines, adhesion molecules, chemokines and some inflammatory-related enzymes. Therefore, much attention has been given to identifying chemical compounds specifically targeting this pathway. NF-κB activation is commonly determined in cellular assays by evaluating the NF-κB/DNA binding activity, the level of NF-κB subunit expression in the nucleus (e.g. p50/p65 subunit), the level of NF-κB phosphorylation, the level of NF-κB-mediated gene expression, the extent of NF-κB-dependent gene reporter binding activities, NF-κB luciferase activity, the presence of IκBα degradation, IKK activity and the presence of NF-κB mobilization (e.g. nuclear translocation of p50/p65 subunit). Another related pathway is *via* PPARs, a group of nuclear receptors often interacting with the NF-κB signalling pathways. It has been shown that NF-κB activity is negatively regulated by PPAR activators which have been reported to inhibit the activation of the inflammatory response [391]. PPAR activities are often evaluated by examining the PPAR ligand binding

Table 3. Medicinal Plants and Nutraceuticals for the Treatment of Diabetic Complications with Clinical and Animal Evidences

Medicinal Plant/ Nutraceuticals	Common Name	Beneficial Effects in Diabetic Complications	Level of Scientific Evidence	References
Allium sativum	Garlic	• Diabetic nephropathy • Anti-oxidative effect • Diabetic cardiovascular complications	Animal studies Animal studies Animal studies	[57-59]
Aloe vera	Aloe	• Anti-inflammatory effect • Diabetic wound healing • Diabetic nephropathy • Anti-oxidative effect	Animal studies Animal studies Animal studies Animal studies	[60-65]
Angelica sinensis	-	• Diabetic peripheral neuropathy	Animal studies	[66]
Astragalus membranaceus	Huang qi	• Diabetic nephropathy • Diabetic microangiopathy • Anti-inflammatory effect	Medium/Animal studies Medium Animal studies	[67-70]
Capsicum frutescens	Capsicum	• Diabetic neuropathy	High	[71-75]
Carica papaya	Papaya	• Diabetic wounds	Animal studies	[76]
Camellia sinensis	Green tea	• Diabetic nephropathy • Diabetic cataract • Diabetic retinopathy • Anti-oxidative effects	Animal studies Animal studies Animal studies Animal studies	[77-85]
Centella asiatica	Gotu Kola	• Diabetic microangiopathy and oedema • Diabetic wound healing	High Animal studies	[86-88]
Cinnamonum cassia	Cinnamon	• Anti-oxidative effect	Animal studies	[89]
Cinnamomum zeylanicum	Cinnamon	• Diabetic nephropathy	Medium	[90]
Colocassia esculenta	Dasheen	• Diabetic nephropathy	Animal studies	[91]
Curcuma longa	Turmeric	• Anti-oxidative effect • Diabetic retinopathy	Animal study Animal study	[92, 93]
Dioscorea cayenensis	Yam	• Diabetic nephropathy	Animal studies	[91]
Eugenia jambolana/ Syzgium cumini	Jambul	• Diabetic neuropathy • Diabetic nephropathy • Diabetic gastropathy • Diabetic cataract • Ulcer healing • Anti-oxidative effect	Animal studies Animal studies Animal studies Animal studies Animal studies Animal studies	[94-101]
Fish oil	-	• Endothelial function • Anti-oxidative effects • Diabetic nephropathy • Anti-inflammatory effect	High Medium Animal studies High/Animal studies	[102-105]
Ganoderma lucidum	Lingzhi mush-room	• Diabetic nephropathy	Animal studies	[106]
Ginkgo biloba	Ginkgo	• Diabetic retinopathy • Diabetic nephropathy • Endothelial dysfunction	Medium High/Animal High	[107-111]

(Table 3) Contd….

Medicinal Plant/ Nutraceuticals	Common Name	Beneficial Effects in Diabetic Complications	Level of Scientific Evidence	References
Glycine max	Soybean	• Improves major and emerging cardiovascular risk factors and diabetic nephropathy	Medium	[112]
Gymnema montanum	-	• Diabetic nephropathy • Anti-oxidative effect	Animal studies Animal studies	[113, 114]
Gynostemma pentaphyllum	Jiaogulan	• Diabetic cardiomyopathy	Animal studies	[50]
Honey	-	• Wound healing • Anti-oxidative effect	Medium Animal studies	[115, 116]
Juglans regia	Walnut	• Anti-oxidative effect	Medium	[117]
Linum usitatissimum	Flaxseed/ linseed	• Anti-inflammatory effects • Diabetic nephropathy	High Animal studies	[118-120]
Lycium barbarum	Wolfberry	• Anti-oxidative effect	Animal studies	[121]
Medicago sativa	Alfalfa	• Anti-inflammatory	Animal studies	[122, 123]
Momordica charantia	Bitter melon	• Diabetic wound healing • Anti-oxidative effect • Diabetic nephropathy • Diabetic cataract	Animal studies Animal studies Animal studies Animal studies	[98, 99, 124-129]
Oenothera biennis	Evening primrose	• Diabetic neuropathy	Animal studies	[130]
Olea europaea	Olive	• Diabetic nephropathy • Anti-oxidative effects	Animal studies Animal studies	[131, 132]
Paeonia suffruticosa	Peony	• Diabetic cataract	Animal studies	[133]
Panax ginseng	Ginseng	• Anti-inflammatory • Diabetic nephropathy	Animal studies Animal studies	[134, 135]
Panax notoginseng	Tienchi ginseng	• Diabetic nephropathy • Diabetic macroangiopathy • Anti-oxidative effect	Medium/ Animal studies Medium Animal studies	[68, 136-139]
Pinus pinaster	Maritime pine	• Diabetic retinopathy • Diabetic microangiopathy • Diabetic ulcer	High High Medium	[140-142]
Polygonatum odoratum	Solomon's seal	• Diabetic nephropathy	Animal studies	[143]
Propolis	-	• Diabetic foot ulcer • Diabetic nephropathy	General/Animal studies Animal studies	[144-146]
Pueraria lobata	Kudzu	• Anti-oxidative effect	Animal studies	[147]
Punica granatum	Pomegranate	• Diabetic cardiovascular disease • Anti-oxidative effect • Anti-inflammatory effect • Endothelial function	Medium/Animal studies Medium/Animal studies Animal studies Animal studies	[148-155]
Rehmannia glutinosa	Sheng di huang	• Diabetic foot ulcer • Anti-oxidative effect	Animal studies Animal studies	[156, 157]
Rheum officinale	Rhubarb	• Diabetic nephropathy	Animal studies	[158]

(Table 3) Contd….

Medicinal Plant/ Nutraceuticals	Common Name	Beneficial Effects in Diabetic Complications	Level of Scientific Evidence	References
Rhodiola rosea	Golden root	• Anti-oxidative effect	Animal studies	[89]
Salvia hispanica	Chia	• Improves major and emerging cardiovascular risk factors	High	[159]
Salvia miltiorrhiza	Danshen	• Diabetic foot ulcer • Diabetic vascular disease • Diabetic nephropathy • Anti-oxidative effects	High Medium Animal studies Animal studies	[160-163]
Silybum marianum	Milk thistle	• Diabetic nephropathy	Animal studies	[164]
Tinospora cordifolia	Guduchi	• Diabetic foot ulcers • Diabetic neuropathy and gastropathy	High Animal studies	[97, 165]
Trigonella foenum graecum	Fenugreek	• Diabetic retinopathy	Animal studies	[166]
Vaccinium myrtillus	Bilberry	• Diabetic retinopathy	Animal studies	[167]
Vitis vinifera	Grape	• Anti-inflammatory and anti-oxidative effects • Diabetic nephropathy • Diabetic neuropathy • Diabetic macrovascular disease • Diabetic retinopathy	High Animal studies Animal studies Animal studies Animal studies	[164, 168-174]
Withania somnifera	Ashwagandha	• Anti-oxidative effects	Animal studies	[175, 176]
Zingiber officinale	Ginger	• Anti-inflammatory effects/diabetic neuropathy	Animal studies	[177]

Note : Classification of the level of scientific evidence are mentioned in Table **2**. "High" level for systematic reviews or randomised controlled trials. "Medium" level for pseudo-randomised controlled trials, comparative studies with concurrent controls or comparative studies without concurrent controls. "General" level for case series. Animal studies are ranked 4 in this scale.

Table 4. Phytochemicals Against Diabetic Complications with Clinical and Animal Evidences

Phytochemical	Example of Source	Beneficial Effects in Diabetic Complications	Level of Scientific Evidence	References
Astilbin	*Hypericum perforatum* *Taxillus kaempferi*	• Diabetic nephropathy	Animal studies	[178]
Astragaloside IV	*Astragalus membranaceus*	• Diabetic peripheral neuropathy	Animal studies	[179]
Astragalus saponin I	*Astragalus membranaceus*	• Diabetic nephropathy	Animal studies	[180]
Baicalein	*Scutellaria baicalensis*	• Diabetic retinopathy	Animal studies	[181]
Berberine	*Coptis chinensis*	• Diabetic nephropathy	Animal studies	[182]
Breviscapine	*Erigerin breviscapus*	• Diabetic nephropathy	Animal studies	[183]
Curcumin	*Curcuma longa*	• Diabetic nephropathy • Diabetic neuropathy • Diabetic wound healing • Diabetic retinopathy	Animal studies Animal studies Animal studies Animal studies	[93, 184-188]
Delphinidin	*Punica granatum* *Vitis vinifera*	• Diabetic microangiopathy	Animal studies	[189]
Docosahexanoic acid	Fish oil	• Diabetic retinopathy	Animal studies	[190]

(Table 4) Contd….

Phytochemical	Example of Source	Beneficial Effects in Diabetic Complications	Level of Scientific Evidence	References
Epigallocatechin gallate	*Camellia sinensis* *Punica granatum* *Vitis vinifera*	• Diabetic nephropathy • Enhanced wound healing • Endothelial function	Animal studies Animal studies Animal studies	[191-193]
Eugenol	*Syzygium aromaticum* *Cinnamomum zeylanicum*	• Diabetic neuropathy • Diabetic vasculopathy	Animal studies Animal studies	[194]
Genistein	*Glycine max*	• Diabetic retinopathy	Animal studies	[195]
Isoliquiritigenin	*Glycyrrhiza glabra*	• Diabetic neuropathy	Animal studies	[196]
γ-linolenic acid	*Oenothera biennis*	• Diabetic peripheral neuropathy	High	[197]
α-lipoic acid	*Spinacia oleracea*	• Endothelial dysfunction	Animal studies	[198]
Lithospermate B	*Salvia miltiorrhiza*	• Diabetic nephropathy	Animal studies	[199]
Lithospermic acid B	*Salvia miltiorrhiza*	• Diabetic nephropathy	Animal studies	[200]
Lycium barbarum polysaccharide 4	*Lycium barbarum*	• Diabetic nephropathy	Animal studies	[201]
Magnolol	*Magnolia officinalis*	• Diabetic nephropathy	Animal studies	[202]
Maltol	*Larix europoea*	• Diabetic nephropathy	Animal studies	[203]
Mangiferin	*Anemarrhena asphodeloides* *Mangifera indica*	• Atherosclerosis • Diabetic nephropathy	Animal studies Animal studies	[204, 205]
Oleanolic acid	*Olea europaea*	• Diabetic nephropathy	Animal studies	[206]
Protocatechualdehyde	*Salvia miltiorrhiza*	• Diabetic cataract	Animal studies	[207]
Puerarin	*Pueraria lobata*	• Diabetic vasculopathy • Diabetic retinopathy	Animal studies Animal studies	[208, 209]
Quercetin	*Punica granatum* *Centella asiatica*	• Diabetic nephropathy • Diabetic neuropathy	Animal studies Animal studies	[210-212]
Resveratrol	*Vitis vinifera* *Propolis*	• Diabetic neuropathy	Animal studies	[185, 213]
Rhein	*Rheum palmatum* *Rheum officinale*	• Diabetic nephropathy	Animal studies	[214]
Rutin	*Rheum palmatum* *Rheum officinale*	• Diabetic nephropathy	Animal studies	[215]
Scoparone	*Artemisia scoparia*	• Atherosclerosis	Animal studies	[216]
Scutellarin	*Scutellaria baicalensis* *Erigeron multiradiatus*	• Vascular inflammation	Animal studies	[217]
α-spinasterol	*Phytolacca americana*	• Diabetic nephropathy	Animal studies	[218]
Tanshinone IIA	*Salvia miltiorrhiza*	• Diabetic nephropathy	Animal studies	[219]
Tetrandrine	*Stephania tetrandra*	• Diabetic choroidal angiogenesis	Animal studies	[220]
Troxerutin	*Sophora japonica*	• Diabetic retinopathy	Animal studies	[221]
Vitamin E	*Asparagus officinalis* *Spinacia oleracea*	• Endothelial dysfunction	Animal studies	[222]

Note : Classification of the level of scientific evidence are mentioned in Table **2**. "High" level for systematic reviews or randomised controlled trials. "Medium" level for pseudo-randomised controlled trials, comparative studies with concurrent controls or comparative studies without concurrent controls. "General" level for case series. Animal studies are ranked 4 in this scale.

Table 5. Anti-Inflammatory and Anti-Oxidative Activities of Representative Phytochemicals

Chemical Group	Subgroup	Phytochemical	Example of Source	Modulate Inflammation	Anti-Oxidative Activities
Lipids	Fatty acids and lipids	Oleic acid	*Vitis vinifera* *Olea europaea* *Punica granatum*	[223, 224]	[223]
	Hydrocarbons and derivatives	Allicin	*Allium sativum*	[225-228]	[226, 227]
		Diallyl disulfide	*Allium sativum*	[229, 230]	[229]
		Diallyl trisulfide	*Allium sativum*	[229-231]	[229, 232]
Nitrogen containing compounds	Alkaloids	Berberine	*Coptis chinensis*	[233-237]	[235, 238]
		Piperine	*Piper longum* *Piper nigrum*	[239-241]	[242]
	Non-alkaloids	N-(p-coumaroyl)serotonin	*Carthamus tinctorius* *Amorphophallus konjac* *Echinochloa utilis* *Centaurea nigra*	[243]	[243]
		N-feruloylserotonin	*Carthamus tinctorius* *Amorphophallus konjac* *Echinochloa utilis* *Centaurea nigra*	[243]	[243]
Phenolic compounds	Anthochlor	Chalcone	*Angelica keiskei*	[244]	[245]
	Diarylheptanoids	5-*O*-methylhirsutanonol	*Alnus japonica*	[246, 247]	[246]
	Catechin	Epigallocatechin gallate	*Camellia sinensis* *Punica granatum* *Vitis vinifera*	[248-254]	[255-257]
	Flavones and Flavonols	Apigenin	*Chrysanthemum morifolium* *Punica granatum* Propolis	[258-267]	[267]
		Chrysin	Propolis	[258, 261-263, 268, 269]	[270]
		Kaempferol	*Punica granatum* *Centella asiatica*	[258, 261-263, 265, 268, 271-273]	[274, 275]
		Luteolin	*Chrysanthemum morifolium* *Punica granatum*	[258, 261, 263-267, 276, 277]	[267, 270]
		Myricetin	*Punica granatum*	[258, 272, 273, 278]	[279]
		Quercetin	*Punica granatum* *Centella asiatica*	[258, 261, 264, 265, 268, 271, 273, 278, 280-283]	[275, 284]
		Scutellarin	*Scutellaria baicalensis* *Erigeron multiradiatus*	[217]	[285]
		Wogonin	*Scutellaria baicalensis*	[281, 286-294]	[295, 296]
	Lignans	Magnolol	*Magnolia officinalis*	[297-301]	[301]
	Phenols and phenolic acids	Cannabidiol	*Cannabis sativa*	[25, 302, 303]	[304]

(Table 5) Contd….

Chemical Group	Subgroup	Phytochemical	Example of Source	Modulate Inflammation	Anti-Oxidative Activities
		Ellagic acid	*Juglans regia* *Punica granatum* *Vitis vinifera* *Vaccinium myrtillus*	[305, 306]	[307]
		Gallates (e.g. methyl gallate, ethyl gallate, propyl gallate, octyl gallate)	*Punica granatum*	[308]	[309-312]
		Hydroxytyrosol	*Olea europaea*	[313-315]	[316-318]
		Protocatechualdehyde	*Salvia miltiorrhiza*	[319]	[320]
	Phenolic ketones	Hematein	*Caesalpinia sappan*	[321, 322]	[321]
		Paeonol	*Cortex moutan* *Paeonia lactiflora*	[323-327]	[323]
	Phenylpropanoid	Caffeic acid	*Punica granatum* Propolis	[328]	[329-331]
		Chlorogenic acid	*Punica granatum*	[332-334]	[334]
		Cinnamaldehyde	*Cinnamomum cassia* *Cinnamomum zeylanicum*	[335-337]	[335]
		Curcumin	*Curcuma longa*	[338-347]	[348]
	Stilbenoids	Resveratrol	*Vitis vinifera* Propolis	[261, 314, 349-358]	[359, 360]
Terpenoids	Iridoids	Cornuside	*Cornus officinalis*	[361]	[362]
		Oleuropein	*Olea europaea*	[314, 363]	[316, 363]
	Sesquiterpene lactones	Bisacurone	*Curcuma longa*	[364]	[364]
		Parthenolide	*Tanacetum parthenum*	[259, 365-370]	[371]
	Diterpenoids	Cryptotanshinone	*Salvia miltiorrhiza*	[372-374]	[375]
		Ginkgolide B	*Ginkgo biloba*	[376]	[376]
		Tanshinone IIA	*Salvia miltiorrhiza*	[377-380]	[375, 381]
	Triterpenoid saponins	Astragaloside IV	*Astragalus membranaceus*	[382]	[383]
		Gypenoside XLIX	*Gynostemma pentaphyllum*	[47, 49]	ND
	Steroid saponins	Ruscogenin	*Ruscus aculeatus* *Radix ophiopogon*	[384, 385]	ND
	Phytosterols	β-Sitosterol	*Punica granatum* *Lycium barbarum* *Centella asiatica* *Zea mays* *Glycine max*	[386, 387]	[388]
	Miscellaneous triterpe-noids	Betulinic acid	*Lycopus lucidus* *Rhododendron arboreum* *Punica granatum*	[389]	[389, 390]

ND- no data available

activities, PPAR reporter activities, the expression of PPAR target gene and the level of PPAR expression. Based on these results, many phytochemicals with distinctive chemical structures have been evaluated as potential inhibitors for NF-κB activation. Several representative phytochemical inhibitors of NF-κB from each chemical class, which also exhibited positive effects against vascular inflammation with/without PPAR activities, are summarized in Table **6**. The major chemical classes include phenolic compounds, terpenoids, nitrogen containing compounds and lipids.

The majority of phytochemicals isolated from natural products that inhibit NF-κB activation are phenolic compounds. Phenolic compounds are characterized by an aromatic ring with the presence of hydroxyl groups. They often possess strong anti-oxidant power. Therefore, they tend to be considered beneficial for general health and well-being. Several phenolic compounds from different subgroups have been selected to be discussed below in detail including flavones and flavanols (e.g. apigenin, chrysin, kaempferol, luteolin, myricetin, quercetin and wogonin), lignans (e.g. magnolol), phenols and phenolic acids (e.g. cannabidiol, ellagic acid and protocatechualdehyde), phenylpropanoids (e.g. caffeic acid, chlorogenic acid, cinnamaldehyde and curcumin), catechins (e.g. epigallocatechin-3-gallate) and stilbenoids (e.g. resveratrol) (Fig. **3**). Other phytochemicals from different subgroups have also been discussed, such as diterpenoids (e.g. cryptotanshinone and tanshinone IIA), sesquiterpene lactone (e.g. parthenolide), triterpenoid saponin (e.g. astragaloside IV), steroid saponins (e.g. Ruscogenin), phytosterol (e.g. β-sitosterol), miscellaneous triterpenoids (e.g. betulinic acid), alkaloids (e.g. berberine and piperine), and fatty acids and lipids (e.g. oleic acid) (Figs. **4**-**6**).

4.2.1. Flavones and Flavonols

Apigenin, chrysin, kaempferol, luteolin, myricetin and quercetin belong to the group of flavones and flavonols. These compounds are widely regarded as strong anti-oxidants. They are commonly found in many plants and natural products, such as *Centella asiatica*, pomegranate and propolis. Foods rich in these flavones and flavonols reduced coronary heart disease mortality in elderly men [392]. Several studies demonstrated that these phytochemicals were capable of suppressing NF-κB activation. Apigenin and luteolin influenced NF-κB signalling pathways by inhibiting IKK activity, IκBα degradation, NF-κB-DNA binding activity, nuclear translocation of NF-κB p65 subunit and NF-κB luciferase activity [263, 264, 276]. Chrysin and kaempferol reduced TNF-α induced NF-κB luciferase activity, IKK activity, NF-κB-DNA binding activity and IκBα degradation; in addition to these effects, chrysin also suppressed the nuclear translocation of p65 subunit [263, 269, 271]. Studies have also evaluated the inhibitory effects of quercetin and myricetin on NF-κB activation; both compounds attenuated the nuclear translocation of p65 subunit and NF-κB-DNA binding activity, whilst myricetin also diminished NF-κB luciferase activity [264, 271, 278]. Apigenin, chrysin, kaempferol, luteolin, myricetin and quercetin have been reported to disrupt the production of adhesion molecules which is regulated by NF-κB. Apigenin and luteolin suppressed the expressions of VCAM-1, ICAM-1 and E-selectin at transcriptional and protein levels, and also blocked the ability of monocytes adherence to the endothelial monolayer [258, 263-267]. Similar effects have also been demonstrated after chrysin, kaempferol, myricetin and quercetin treatments [263-265, 271, 273, 280, 282, 283]. Lotito *et al.* (2006) suggested that the chemical structure of flavonoid required for the inhibition of adhesion molecule expression involved the 5,7-dihydroxyl moiety of A-ring and 2,3-double bond and 4-keto moiety on the C-ring [265]. Indeed, the magnitude for the suppression of monocyte adhesion to endothelial cells by flavonols was linked with the number of hydroxyl moiety on the B-ring [273]. Evidently, these NF-κB-modulating flavones

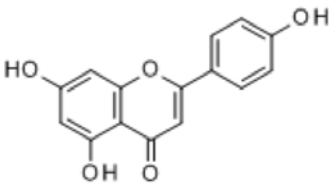
Table 6. Representative Phytochemicals Against Vascular Inflammation and Inflammatory Pathways

Chemical Group	Subgroup	Phytochemical	Leukocyte Recruitment	NF-κB	Pro-inflammatory Cytokine Production	iNOS	PPARs
Lipids	Fatty acids and lipids	Oleic acid	[224]	[223]	ND	[223]	ND
	Hydrocarbons and derivatives	Allicin	[228]	[227]	[226]	[225]	ND
		Diallyl disulfide	[230]	[229]	ND	[229]	ND
		Diallyl trisulfide	[230]	[229]	ND	[229, 231]	ND
Nitrogen containing compounds	Alkaloids	Berberine	[233, 235, 236]	[234, 236]	[233, 234]	[237]	[233]
		Piperine	[239]	[239, 241]	[240]	[240]	ND
	Non-alkaloids	N-(p-coumaroyl)serotonin	[243]	[243]	ND	ND	ND
		N-feruloylserotonin	[243]	[243]	ND	ND	ND
Phenolic compounds	Anthochlor	Chalcone	[244]	[244]	ND	ND	ND
	Diarylheptanoids	5-*O*-methylhirsutanonol	[247]	[246, 247]	[246]	[246]	ND
	Catechin	Epigallocatechin gallate	[251-254]	[248, 251]	[248]	[249]	[250]
	Flavones and Flavonols	Apigenin	[258, 263-267]	[263, 264]	[258-261]	[260-262]	[262]
		Chrysin	[258, 263]	[269]	[261, 268]	[261, 262, 268]	[262]
		Kaempferol	[258, 263, 265, 271, 273]	[271]	[261, 268]	[261, 262, 268, 271, 272]	[262]

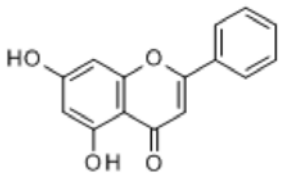
(Table 6) Contd….

Chemical Group	Subgroup	Phytochemical	Leukocyte Recruitment	NF-κB	Pro-inflammatory Cytokine Production	iNOS	PPARs
		Luteolin	[258, 263-267, 276]	[263, 264, 276]	[261, 276]	[261]	[277]
		Myricetin	[258, 273]	[278]	[278]	[272]	ND
		Quercetin	[258, 264, 265, 271, 273, 280, 282, 283]	[264, 271]	[261, 268, 278, 280]	[261, 268, 271, 281]	[280]
		Scutellarin	[217]	[217]	ND	ND	ND
		Wogonin	[288, 293, 294]	[286, 287, 291-293]	[286-288]	[281, 286, 289, 290]	ND
	Lignans	Magnolol	[297, 299-301]	[297, 299, 300]	ND	[297]	[298]
	Phenols and phenolic acids	Cannabidiol	[25]	[25, 302]	[302, 303]	[25]	ND
		Ellagic acid	[305, 306]	[305]	ND	ND	ND
		Gallates (e.g. methyl gallate, ethyl gallate, propyl gallate, octyl gallate)	[308]	[308]	ND	ND	ND
		Hydroxytyrosol	[314]	[314]	[315]	[315]	[313]
		Protocatechualdehyde	[319]	[319]	ND	ND	ND
	Phenolic ketones	Hematein	[322]	[321, 322]	ND	[321]	ND
		Paeonol	[326, 327]	[324, 326]	[323, 325]	[324]	ND
	Phenylpropanoids	Caffeic acid	[328]	[328]	ND	ND	ND
		Chlorogenic acid	[332, 334]	[334]	[332]	ND	[333]
		Cinnamaldehyde	[337]	[337]	[335]	[336]	ND
		Curcumin	[341, 347]	[339-346]	[338, 339]	[340]	[338]
	Stilbenoids	Resveratrol	[357, 358]	[314, 349, 353, 355-357]	[261, 349, 350]	[261, 349]	[350-354]
Terpenoids	Iridoids	Cornuside	[361]	[361]	ND	ND	ND
		Oleuropein	[314]	[314]	ND	[363]	ND
	Sesquiterpene lactones	Bisacurone	[364]	[364]	ND	ND	ND
		Parthenolide	[369]	[367-370]	[259]	[365-368]	ND
	Diterpenoids	Cryptotanshinone	[372]	[372, 374]	[372, 374]	[373]	ND
		Ginkgolide B	[376]	[376]	ND	ND	ND
		Tanshinone IIA	[380]	[379]	[377]	[377, 378]	ND
	Triterpenoid saponins	Astragaloside IV	[382]	[382]	ND	ND	ND
		Gypenoside XLIX	[49]	[47]	ND	ND	[47, 48]
	Steroid saponins	Ruscogenin	[384, 385]	[384, 385]	ND	ND	ND
	Phytosterols	β-Sitosterol	[386, 387]	[387]	ND	ND	ND
	Miscellaneous triterpenoids	Betulinic acid	[389]	[389]	ND	ND	ND

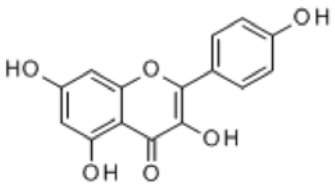
ND- no data available



(a) Apigenin



(b) Chrysin



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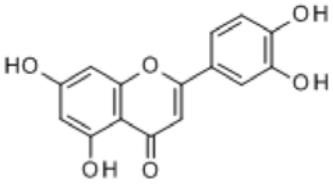
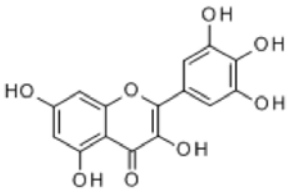
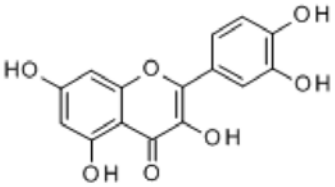


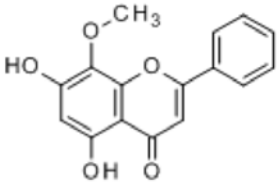
(d) Luteolin



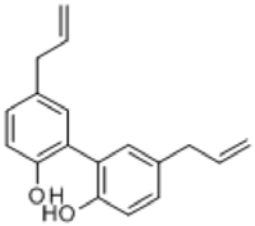
(e) Myricetin



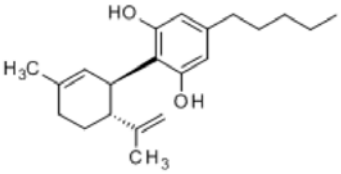
(f) Quercetin



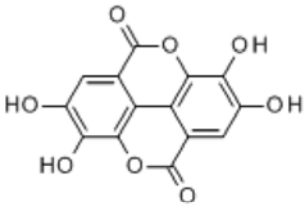
(g) Wogonin



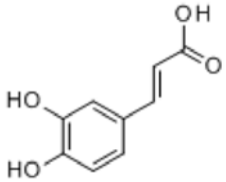
(h) Magnolol



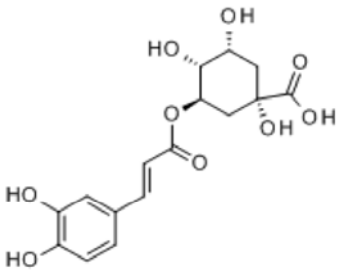
(i) Cannabidiol



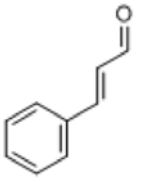
(j) Ellagic acid



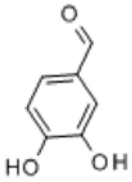
(k) Caffeic acid



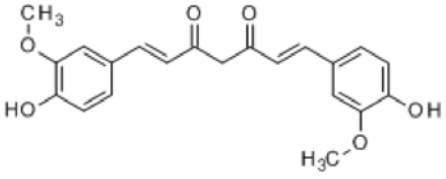
(l) Chlorogenic acid



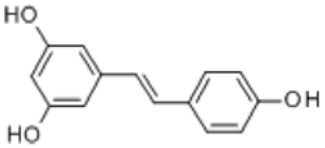
(m) Cinnamaldehyde



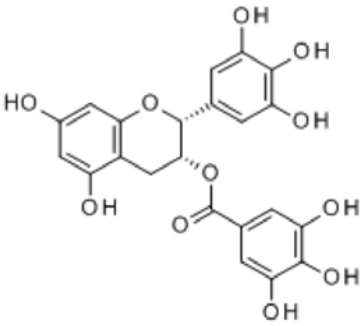
(n) Protocatechualdehyde



(o) Curcumin

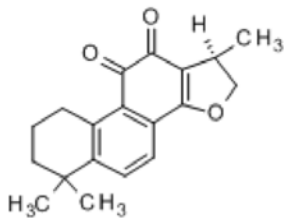


(p) Resveratrol

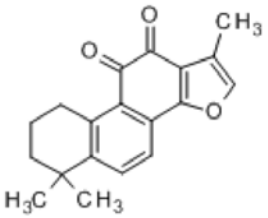


(q) Epigallocatechin gallate

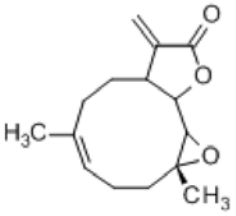
Fig. (3). Chemical structures of some phenolic compounds.



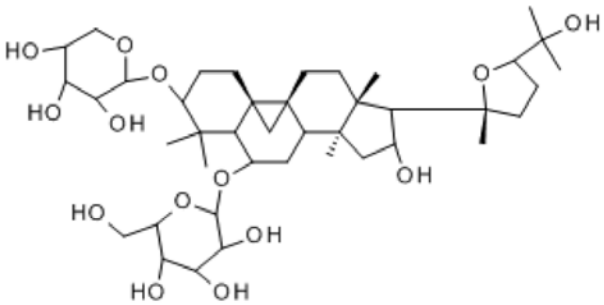
(a) Cryptotanshinone



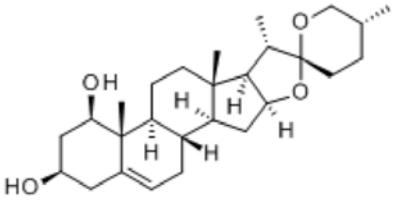
(b) Tanshinone IIA



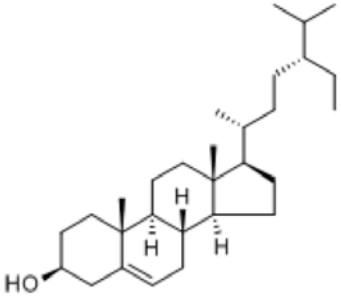
(c) Parthenolide



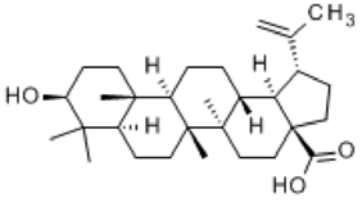
(d) Astragaloside IV



(e) Ruscogenin

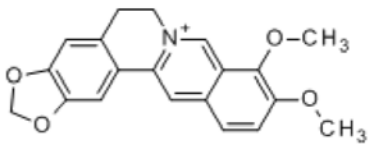


(f) β-sitosterol

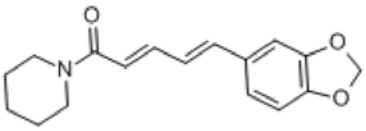


(g) Betulinic acid

Fig. (4). Chemical structures of some terpenoids.

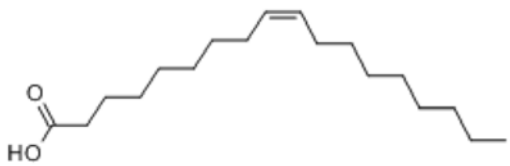


(a) Berberine



(b) Piperine

Fig. (5). Chemical structures of some nitrogen containing compounds.



Oleic acid

Fig. (6). Chemical structure of Oleic acid.

and flavonols, apigenin, chrysin, kaempferol, luteolin, myricetin and quercetin also influenced other NF-κB-regulated inflammatory responses, such as the production of pro-inflammatory cytokines and iNOS [258-262, 268, 271, 272, 276, 278, 280, 281]. In particular, apigenin significantly blocked the production of TNF-α, IL-1β, IL-6, IL-8 and IL-12 in several cell lines, including TNF-α-activated endothelial cells, lipopolysaccharide (LPS) activated RAW 264.7 macrophages, and nicotine- and LPS-activated human periodontal ligament cells, as well as in *in vivo* rodent models, LPS-stimulated female B6C3F1 mice [258-261]. Apigenin blocked iNOS expression in LPS-activated RAW 264.7 macrophages, and also inhibited LPS-induced NO production in human periodontal

ligament cells, partially by attenuating iNOS promoter activity and the up-regulation of iNOS [260-262]. In addition, it was further confirmed that PPARs down-regulated inflammatory events by interacting with NF-κB signalling pathways. Liang *et al.* (2001) suggested that apigenin, chrysin and kaempferol inhibited iNOS promoter activity, which was dependent on the expressions of PPAR-γ [262]. Luteolin and quercetin also increased PPAR-γ activities and therefore their anti-inflammatory effects may be dependent on their activities on PPAR-γ expression [277, 280]. In summary, the above mentioned flavones and flavonols may treat diabetic vascular complications by suppressing vascular inflammation through NF-κB signalling pathways.

Wogonin, originally isolated from *Scutellaria baicalensis*, is one of the 50 fundamental herbs in traditional Chinese Medicine in a recipe for treating inflammation, fever and headache [393]. Wogonin inhibited NF-κB activation, partially by suppressing NF-κB-DNA-binding activity and nuclear translocation of p65 subunit [286, 287, 292]. Chang *et al.* (2001) demonstrated that wogonin blocked the phorbol-12 myristate 13-acetate -induced mRNA and protein expression of chemokines, MCP-1, in human umbilical vein endothelial cells (HUVEC) [294]. In addition, a previous study reported the inhibition of MCP-1 release in LPS-stimulated microglial cells and MCP-1-induced migration of microglial cells, with wogonin produce similar effects to other known NF-κB inhibitors [293]. This study demonstrated the role of NF-κB in regulating cell migration. Unsurprisingly, other NF-κB-regulated inflammatory responses were also affected by wogonin treatment. For example, wogonin weakly blocked the gene expression of IL-1β, whilst the expressions of TNF-α, IL-6 and IL-8 were significantly attenuated at the transcriptional and protein levels [286-288]. Furthermore, the mRNA expression of ICAM-1 was moderately suppressed in 12-O-tetradecanoylphorbol 13-acetate (TPA)-stimulated ear skin tissue [288]. Lastly, many studies pointed out that wogonin inhibited NO production, partially by blocking iNOS induction and production [281, 286, 290]. As a result, these effects illustrated the extensive role of wogonin in modulating vascular inflammation.

4.2.2. Lignans

Magnolol is a naturally occurring lignan in *Magnolia officinalis*. Chen *et al.* (2001) demonstrated that the formation of atherosclerotic lesion area of the thoracic aorta and the intimal thickening in the abdominal aortas after balloon injury were significantly attenuated after magnolol treatment in cholesterol-fed rabbits. Interestingly, the expression of MCP-1 mRNA and its protein expression were significantly reduced in the abdominal aorta [300]. The same research group also showed that magnolol significantly attenuated the protein expression of VCAM-1 in human aortic endothelial cells after TNF-α stimulation and the adherence of monocytes to endothelial monolayer. It was considered that these effects may be mediated by the inhibition of NF-κB and nuclear translocation of NF-κB p65 subunit [299]. Using the same animal model, it was found that magnolol reduced intimal thickening and the protein expressions of TNF-α and VCAM-1 in the thoracic aorta [299]. In addition, the effects of magnolol on NF-κB have been evaluated by Tse *et al.* (2007), who found that magnolol blocked the activation of NF-κB in human histiocytic lymphoma (U937) cells, human promyelocytic leukaemia (HL-60) cells, human breast epithelial (MCF-7) cells and human cervix epithelial (HeLa) cells [297]. It was explained that these effects may be mediated by inhibiting IκBα phosphorylation and degradation, IKK activity, nuclear translocation of NF-κB p65 subunit and NF-κB-regulated gene expression (e.g. MCP-1) [297]. Moreover, the mRNA and protein expressions of iNOS (a protein known to be regulated by NF-κB), were reduced in TPA stimulated mouse skin [297]. These anti-inflammatory effects may be linked with its action on PPARs, as magnolol activated PPAR-γ in 3T3-L1 adipocytes, possibly acting as a ligand for PPAR-γ receptors and resulting in improved insulin sensitivity [298].

4.2.3. Phenols and Phenolic Acids

Cannabidiol is a phenolic constituent originally isolated from marijuana (*Cannabis sativa*) and widely instigated in drug abuse. Cannabidiol has been reported to exhibit anti-microbial and anti-bacterial properties. Rajesh *et al.* (2007) evaluated its effects on vascular inflammation and found that high glucose stimulated the expressions of adhesion molecules (VCAM-1 and ICAM-1) and iNOS in human coronary artery endothelial cells [25]. These up-regulation effects were attenuated by cannabidiol, together with the reduction in monocyte adhesion and monocyte trans-endothelial migration, which could be mediated by inhibiting the activation of NF-κB. This is due to cannabidiol blocking the translocation of NF-κB p65 subunit to the nucleus, p65 subunit phosphorylation and IκBα degradation [25, 302]. Another study by Napimoga *et al.* (2009) demonstrated that cannabidiol decreased the production of pro-inflammatory cytokines such as IL-1β and TNF-α in gingival tissues [303]. The production and secretion of IL-1β and IL-6 were also reduced by cannabidiol in LPS-activated BV-2 microglial cells [302]. Combining the available findings, cannabidiol should be considered for treating disease conditions linked to vascular inflammation.

Ellagic acid is a phenolic anti-oxidant that can be isolated from many natural products such as bilberry, grape, walnut and pomegranate. Recent studies indicated that ellagic acid is potentially useful in the management of inflammatory disease (e.g. atherosclerosis) and cancer. Researchers have demonstrated that ellagic acid attenuated the protein expression of VCAM-1 and ICAM-1 in TNF-α-stimulated human aortic endothelial cells [306]. Similar results were also displayed by Yu *et al.* (2007), indicating that ellagic acid suppressed the expression of VCAM-1 and E-selectin gene, as well as the adherence of monocytes to IL-1β-activated human umbilical vein endothelial cells. Furthermore, these effects may be related to NF-κB inhibition as ellagic acid blocked the nuclear translocations of NF-κB p65 and p50 subunits [305]. These activities demonstrated the beneficial effects of ellagic acid in the management of diabetic vascular complications.

Protocatechualdehyde is a naturally occurring phenolic compound in *Salvia miltiorrhiza*. Zhou *et al.* (2005) demonstrated that protocatechualdehyde down-regulated the mRNA and surface expressions of VCAM-1 and ICAM-1, as well as their soluble form in TNF-α-stimulated HUVEC. The effects are further supported by its ability in the suppression of monocyte adherence to endothelial monolayer. They explained that the effects may be mediated by inhibition of NF-κB, as protocatechualdehyde reduced NF-κB DNA binding activities [319]. These effects may explain the role of protocatechualdehyde in the suppression of inflammation.

4.2.4. Phenylpropanoids

Caffeic acid is a phenolic constituent presented in many natural products including pomegranate and propolis. Current studies by Moon *et al.* (2009) showed that caffeic acid attenuated vascular inflammation. They found that the protein and mRNA expressions of adhesion molecules including VCAM-1, ICAM-1 and E-selectin, chemokines (MCP-1) and pro-inflammatory cytokines (IL-8), were inhibited in TNF-α-stimulated HUVECs, together with the reduction of monocyte adhesion to endothelial monolayers [328]. Indeed, all of these effects can be mediated by NF-κB. As expected, caffeic acid has shown positive effects against IκBα degradation and nuclear translocation of NF-κB p65 subunit, which resulted in the suppression of NF-κB activation [328].

Chlorogenic acid is a naturally occurring phenolic constituent in many plants. Krakauer (2002) demonstrated that chlorogenic acid inhibited the production of pro-inflammatory cytokines (e.g. TNF-α, IL-1β and IL-6) and chemokines (e.g. MCP-1) in human peripheral blood mononuclear cells after staphylococcal exotoxin stimulation [332]. Regarding its effect on the production of adhesion molecules, researchers found that the mRNA expressions of VCAM-1,

ICAM-1 and E-selectin as well as the adherence of monocytes to IL-1β-activated HUVEC, had been attenuated after chlorogenic acid treatment [334]. Significant suppression of NF-κB p50 and p65 subunit translocation to the nucleus was also reported [334]. This offers an explanation of the molecular mechanisms influencing pro-inflammatory cytokines, chemokines and adhesion molecule production. A recent study showed that chlorogenic acid increased the mRNA and protein expression of hepatic PPAR-α in golden hamsters [333]. This indicates that the PPARs activities of chlorogenic acid may interact with the NF-κB signalling pathway and participate in the above mentioned anti-inflammatory effects.

Cinnamaldehyde is a phenylpropanoid constituent found in the stem bark of *Cinnamomum cassia*, which is a fundamental herb in traditional Chinese medicine. Cinnamaldehyde can also be isolated from the bark of a well known spice, cinnamon (*Cinnamomum zeylanicum*). In recent studies, cinnamaldehyde showed inhibitory effects against TNF-α-induced expression of VCAM-1 and ICAM-1 at the transcriptional level, as well as monocyte adhesion to human endothelial monolayer. This was possibly mediated by blocking NF-κB activation through the suppression of IκBα degradation and NF-κB p65 subunit translocation [337]. As expected, cinnamaldehyde also inhibited iNOS expression and NO production in LPS/interferon-γ-stimulated RAW 264.7 cells [336]. In addition, it suppressed the production of pro-inflammatory cytokines (TNF-α and IL-1β) in murine J774A.1 macrophages after LPS or lipoteichoic acid stimulation [335]. These effects demonstrated the potential role of cinnamaldehyde in treating vascular inflammation through NF-κB signalling pathways.

Curcumin, also known as diferuloylmethane, from turmeric (*Curcuma longa*) provides the yellow pigment and flavouring in curry. It belongs to the chemical classes of phenylpropanoids which have potential effects against inflammation and cancer. Pretreatment with curcumin completely blocked the TNF-α-induced expression of adhesion molecules (including VCAM-1, ICAM-1 and E-selectin) in HUVEC. It also attenuated adhesion of monocytes to the TNF-α simulated endothelial cells [341]. Moreover, curcumin reduced iNOS mRNA levels in LPS-activated macrophages [340]. The production of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6, was significantly suppressed by curcumin in carbon tetrachloride-treated rats. Western Blot analysis confirmed the reduced protein production of TNF-α and IL-1β in the liver tissue samples [339]. The decreased expression of TNF-α by curcumin was also observed in septic rats and in endotoxin-activated RAW 264.7 macrophages [338]. These anti-inflammatory effects are known to be mediated by NF-κB. Indeed, many studies demonstrated that curcumin was able to inhibit NF-κB activation in different cell lines and tissues such as murine melanoma (B16F10) cells, human multiple myeloma cells, human myeloid ML-1a cells, RAW 264.7 macrophages, human colon epithelial cells, HUVEC, rat liver tissue and mouse skin. Inhibition of IκBα phosphorylation and degradation, IKK activity, NF-κB p65 subunit translocation, NF-κB-DNA binding and NF-κB transcriptional activity may provide clues to the molecular processes involved [339-346]. In another instance, curcumin up-regulated PPAR-γ expression in liver tissues from cecal ligation- and puncture-treated rats, as well as in endotoxin-stimulated RAW 264.7 macrophages [338]. This effect may further explain the molecular mechanisms of curcumin in inhibiting vascular inflammation.

4.2.5. Stilbenoids

Resveratrol belongs to the group of stilbenoids, a naturally occurring anti-oxidant in grapes, red wine and propolis. The consumption of resveratrol may be useful in the treatment of cardiovascular disease and cancer. Recent studies have demonstrated its role in vascular inflammation. Resveratrol is known to inhibit the activation of NF-κB, partially by suppressing NF-κB-DNA binding activity in LPS-activated HUVEC, IκBα phosphorylation in both TNF-α-activated macrophages and LPS-activated N9 microglial cells [314, 349, 353]. Researchers suggested that the inhibitory effects of resveratrol on NF-κB activation may also involve other molecular mechanisms, such as inhibition of phosphorylation and nuclear translocation of NF-κB p65 subunit, NF-κB dependent reporter gene transcription and IKK activity [355-357]. Concurrently, several NF-κB-regulated inflammatory responses are also affected by resveratrol, including the expression of adhesion molecules, chemokines, pro-inflammatory cytokines and inflammation-related enzymes. Ferrero *et al.* (1998) found that resveratrol treatment attenuated the expression of adhesion molecules including VCAM-1 and ICAM-1 in TNF-α-stimulated HUVEC and LPS-stimulated human saphenous vein endothelial cells. The adherence of monocytes to LPS-stimulated human saphenous vein endothelial cells was also significantly inhibited by resveratrol. In addition, it reduced the neutrophil adhesion of TNF-α-stimulated human EA.hy926 endothelial cells [358]. More recently, similar results were also displayed by Carluccio *et al.* (2003). Studies showed that resveratrol inhibited the expression of VCAM-1, ICAM-1 and E-selectin, as well as monocyte adhesion to HUVEC after the LPS stimulation. The effects of resveratrol on VCAM-1 expression were found to be independent of the stimuli for endothelial cells activations as similar effects were observed using different stimuli to activate the cells, including LPS, TNF-α and PMA [314]. Interestingly, resveratrol suppressed TNF-α-stimulated VCAM-1 promoter activity, indicating the relevance of the NF-κB signalling pathway [314]. Another NF-κB-related inflammatory response, the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β), chemokines (MCP-1), nitric oxide and iNOS were blocked after resveratrol treatment in different cell lines [261, 349, 350, 357]. Finally, researchers showed that resveratrol up-regulated the expression of PPAR-α and -γ, activated PPAR-α and –γ reporters, enhanced PPAR-γ-mediated responses and activated peroxisome proliferator response element reporter [350-354]. Its effects on PPARs may be related to its inhibitory effects against NF-κB and inflammation since the activities of NF-κB are known to be down-regulated by PPARs.

4.2.6. Catechins

Epigallocatechin gallate is a catechin constituent in green tea (*Camellia sinensis*). Current findings showed strong potential for epigallocatechin gallate in modulating vascular inflammation. Epigallocatechin gallate can block the production of pro-inflammatory cytokines, adhesion molecules, chemokines and inflammatory-related enzymes. Chae *et al.* (2007) found that epigallocatechin gallate inhibited the protein and mRNA expression of VCAM-1 and ICAM-1 in angiotensin-II-stimulated HUVEC [252]. Similar results were also demonstrated by Ludwig *et al.* (2004), indicating that epigallocatechin gallate suppressed the expression of VCAM-1 at the transcriptional and protein level, as well as the adherence of monocytes to endothelial monolayer after TNF-α or IL-1β stimulation [254]. Furthermore, the expression of MCP-1 was attenuated after epigallocatechin gallate in both TNF-α-activated bovine coronary microvascular endothelial cells and PMA-activated human endothelial ECV304 cells [251, 253]. Hong *et al.* (2007) further demonstrated that epigallocatechin gallate suppressed monocyte migration through endothelial cells monolayer. The researchers explained that these effects may be linked with the inhibition of NF-κB transcriptional activity, reduced NF-κB-DNA binding activity and IκBα phosphorylation [251]. Yang *et al.* (1998) also showed that epigallocatechin gallate inhibited LPS-induced NF-κB-DNA binding activities and the mRNA expression of TNF-α in RAW 264.7 macrophages [248]. Correspondingly, epigallocatechin gallate inhibited the production of TNF-α in LPS-stimulated mouse peritoneal macrophages and also reduced the serum levels of TNF-α in murine model [248]. Interestingly, published work indicated that epigallocatechin gallate enhanced the expression of PPAR-γ protein, which could also be linked to the inhibition of NF-κB activation [250]. Protein expression and activities of another NF-κB-

regulated protein, iNOS, were reduced in IL-1β-stimulated human chondrocytes, together with decreased production of NO [249].

4.2.7. Diterpenoids

Cryptotanshinone and tanshinone IIA are naturally occurring diterpenoids which have shown positive effects in modulating vascular inflammation. The compounds can be found in the root of *Salvia miltiorrhiza*, a fundamental herb used in traditional Chinese medicine therapy to promote blood circulation diabetic complications. Jin *et al.* (2009) demonstrated that cryptotanshinone significantly suppressed the expression of VCAM-1 and ICAM-1 in HUVEC after TNF-α stimulation. They explained that the effects may be mediated by inhibiting NF-κB activation. In the same study, they also found that cryptotanshinone inhibited the production of pro-inflammatory cytokines (e.g. TNF-α, IL-1β and IL-6), possibly by modulating NF-κB activation. This is because cryptotanshinone inhibited the nuclear translocation of NF-κB p65 subunit in ischaemic myocardial tissues [372]. Similar effects were also observed in LPS stimulated RAW 264.7 macrophages by Tang *et al*. [374]. In conjunction with NF-κB activity inhibition, cryptotanshinone also inhibited iNOS-mediated nitric oxide production in LPS-treated RAW 264.7 macrophages [373]. Tanshinone IIA has been shown to block the activation of NF-κB by inhibiting the increase of the NF-κB DNA complex and NF-κB binding activities in LPS-stimulated RAW 264.7 macrophages. These effects were possibly moderated by suppressing the IκBα degradation and IKK pathway [379]. Later, researchers found that tanshinone IIA inhibited the expression of iNOS in the same cellular model [377, 378]. Fan *et al*. (2009) also demonstrated that the LPS-induced production of NO and pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in RAW 264.7 macrophages were reduced after tanshinone IIA treatment [377]. Another noteworthy result has been shown by Fang *et al.* (2007) regarding the potential effects of tanshinone IIA in vascular inflammation. It was observed that tanshinone IIA reduced the serum levels of VCAM-1 and IL-1β, and, more importantly, the size of aortic intimal area in rabbits fed with high fat diet [380]. Overall, cryptotanshinone and tanshinone IIA may be useful in managing diabetic vascular complications.

4.2.8. Sesquiterpene Lactones

Parthenolide is a sesquiterpene lactone constituent in the leaves of feverfew (*Tanacetum (Chrysanthemum) parthenium*). It is commonly used in the management of inflammatory related diseases including arthritis, fever, migraine and asthma. Researchers have found that parthenolide is capable of inhibiting NF-κB activation due to the reduced NF-κB DNA binding activity in LPS-stimulated human vascular smooth muscle cells (VSMCs) and monocytes. In addition, they demonstrated that parthenolide attenuated IκBα degradation and NF-κB p65 subunit translocation to the nucleus in LPS-stimulated human VSMCs. The ability of parthenolide to inhibit the activation of NF-κB was also demonstrated by several studies using different experimental models, such as HeLa cells, rat aortic smooth muscle cells and rat lung tissues. The molecular mechanisms may include attenuating IκBα degradation, IKK activation, NF-κB/DNA binding and nuclear translocation of the NF-κB p65 subunit [367, 368, 370]. Furthermore, the expression of NF-κB-regulated gene (MCP-1 mRNA) was suppressed in LPS-stimulated murine VSMCs. These effects were further supported by the reduction of the serum levels of MCP-1 and the size of aortic lesion in apoE atherosclerotic mice by parthenolide, together with the attenuation of NF-κB transcriptional activation [369]. The promoter activity of the iNOS gene was attenuated by parthenolide in phorbol ester-stimulated THP-1 monocytes, as well as in LPS-stimulated rat aortic smooth muscle cells [366, 367]. Moreover, the mRNA expression of iNOS was reduced in rat thoracic aortas [368]. This may lead to the reduced production of iNOS and NO as displayed in primary rat microglia after LPS-activation [365]. Despite these results, the effect of parthenolide on the production of pro-inflammatory cytokines remains controversial. This is because parthenolide inhibited LPS-induced pro-inflammatory cytokine production of IL-6 and TNF-α in murine RAW 264.7 macrophage cells, however failed to demonstrate the same effects in mice [259]. Nonetheless, parthenolide is still potentially important for the modulation of vascular inflammation.

4.2.9. Triterpenoid Saponins

Astragaloside IV is a triterpenoid saponin originally isolated from *Astragalus membranaceus*, a herb used in traditional Chinese medicine. Zhang *et al.* (2003) reported that Astragaloside IV reduced the expression of VCAM-1 and E-selectin in LPS-stimulated HUVEC, as well as the adherence of monocytes to the endothelial monolayer. In addition, astragaloside IV also inhibited VCAM-1 expression in HUVEC after TNF-α stimulation. Regarding the mRNA expression of VCAM-1 and E-selectin, astragaloside IV suppressed their expressions in both LPS and TNF-α stimulated HUVEC. These effects are probably mediated by the inhibitory effects of astragaloside IV in NF-κB nuclear translocation and DNA binding activity [382].

4.2.10. Steroid Saponins

Ruscogenin belongs to the group of steroid saponins. It was first isolated from the rhizomes of *Ruscus aculeatus*. It is also found in *Radix Ophiopogon japonicas*, an important herb in traditional Chinese medicine for the treatment of diabetes, inflammatory disease and cardiovascular disease [385]. Its effects on vascular inflammation have been reported by Huang *et al.* (2008). Ruscogenin inhibited the expression of TNF-α-induced ICAM-1 mRNA and protein in human umbilical endothelial cells (ECV304). It was suggested that the effect was mediated by the suppression of NF-κB activation as ruscogenin blocked NF-κB p65 nuclear translocation and also decreased NF-κB/DNA binding activity [385]. They also performed a functionality assay for the inhibitory effects of ruscogenin on adhesion molecule production which showed that it potently reduced the adherence of human pro-myelocytic leukaemia cells (HL-60) to endothelial ECV304 cells [384]. Evidently, the succinylated isomers of ruscogenin also demonstrated similar inhibitory effects on ICAM-1 expression and the adherence of HL-60 cells to endothelial ECV304 cells [384].

4.2.11. Phytosterols

β-sitosterol is a naturally occurring phytosterol in plant, structurally similar to cholesterol. Phytosterols are widespread in many plants including wheat germ, sweet corn, wolfberry, soybean, centella and pomegranate. β-sitosterol has been reported to exhibit anti-hyperlipoproteinaemic and anti-inflammatory properties. Current findings evaluated the effects of β-sitosterol on vascular inflammation. Loizou *et al.* (2010) found that β-sitosterol significantly inhibited the expression of VCAM-1 and ICAM-1, as well as monocyte adhesion in TNF-α-stimulated human aortic endothelial cells. They explained that the effects may be mediated by inhibiting the activation of NF-κB as NF-κB p65 subunit phosphorylation was significantly blocked [387]. The suppression of ICAM-1 and MCP-1 expressions by β-sitosterol was also observed in HUVEC after oxidized lipoprotein stimulation, together with the reduction in monocyte chemotactic, migration and adhesion activities to HUVEC [386].

4.2.12. Miscellaneous Triterpenoids

Betulinic acid is a pentacyclic triterpene constituent commonly found in many plants such as the bark of *Rhododendron arboreum* and the leaves of *Lycopus lucidus*. The role of betulinic acid in modulating vascular inflammation has been recently demonstrated by Yoon *et al.* (2010). The authors found that betulinic acid dose-dependently blocked the expressions of adhesion molecules (VCAM-1, ICAM-1 and E-selectin) in TNF-α-stimulated HUVEC. They explained that the effects may be mediated by inhibiting the nuclear translocation of NF-κB p65 subunit and IκBα degradation leading to the suppression of NF-κB activation [389].

4.2.13. Alkaloids

Berberine is an alkaloid constituent originally isolated from *Coptis chinensis*, a widely prescribed herb in traditional Chinese medicine for the treatment of inflammatory-related disease [235]. Wang *et al.* (2009) reported that high glucose stimulated the expression of adhesion molecules (VCAM-1 and ICAM-1), monocyte adhesion and the activation of NF-κB to HUVEC. With the treatment of berberine, all of these effects were significantly suppressed [236]. Berberine blocked MCP-1 expression (another protein which is regulated by NF-κB activation), as well as monocyte adhesion on activated HUVEC after angiotensin-II stimulation [235]. Similar effects were also demonstrated in another study by Chen *et al.* (2008), where results showed that the expression of MCP-1, as well as the secretion of pro-inflammatory cytokines (TNF-α and IL-6), were diminished in acetylated low-density lipoprotein-stimulated macrophages. They explained that these effects may be mediated by enhancing the activities of PPAR-γ, as the addition of PPAR-γ inhibitors attenuated the inhibitory effects of berberine [233]. Furthermore, the production of IL-1β and TNF-α was inhibited by berberine in acetaldehyde-stimulated HepG2 cells; the effects may be mediated by inhibiting NF-κB activation, partially by blocking the degradation of IκBα [234]. Berberine has also been reported to inhibit the expression of iNOS in both *in vitro* and *in vivo* models [237]. Consequently, all published findings suggested that berberine may be beneficial in suppressing vascular inflammation by targeting NF-κB signalling pathway and PPAR-γ.

Piperine belongs to the group of alkaloids. It is commonly found in the family of peppers (Piperaceae) including *Piper nigrum* and *Piper longum*. It is responsible for the hot and pungent taste of peppers. Kumar *et al.* (2007) evaluated the effects of piperine on leukocyte recruitment using endothelial cells isolated from human umbilical cord vein. They demonstrated that piperine inhibited TNF-α-induced adhesion molecule expressions (e.g. VCAM-1, ICAM-1 and E-selectin) and the adhesion of monocytes to the endothelial monolayer. They further showed that this effect may be mediated by the suppression of TNF-α-induced NF-κB activation by inhibiting the nuclear translocation of NF-κB p65 subunits and IκBα degradation [239]. Similar results were also demonstrated in another study showing that the nuclear translocation of NF-κB subunits (p65 and p50) was blocked by piperine in B16F-10 melanoma cells [241]. On the other hand, Pradeep and Kuttan (2003) showed that pro-inflammatory cytokines (TNF-α) production which can be mediated by NF-κB activation, was reduced in both *in-vtiro* and *in vivo* models after piperine treatment. Moreover, the authors found that piperine reduced the production of nitric oxide which was related to its effect against iNOS expressions [240]. Therefore, these findings suggested that piperine is potentially useful to prevent diabetic vascular complications by attenuating vascular inflammation.

4.2.14. Fatty Acids and Lipids

Oleic acid is commonly found in olive (*Olea europaea*) which is known to be beneficial to overall cardiovascular health. With regards to its relationship with vascular inflammation, oleic acid reduced the expression of VCAM-1 mRNA levels, as well as the adherence of monocytoid U937 cells to HUVEC after LPS stimulation, in which the effects were attributed to the inhibition of NF-κB activation [224]. Another study by Oh *et al.* (2009) demonstrated the inhibition of LPS-induced protein expression of iNOS in BV microglial cells by oleic acid. They indicated that the anti-inflammatory effects may be related to the suppression of NF-κB activation and IKK phosphorylation [223].

5. CONCLUSION/ FUTURE DIRECTIONS

Diabetes with its accompanying complications has become a major epidemic throughout the world and the intensity of this crisis is predicted to increase even further in the next 20 years. Insulin resistance has resulted in a chronic hyperglycaemic condition which will ultimately lead to the development of vascular inflammation and the devastating micro- and macrovascular complications of diabetes. Diabetes and its growing list of complications has contributed to astounding morbidity and mortality statistics, and also has a detrimental impact on economic outcomes, especially amongst developing countries. The problem has been exacerbated with the increasing prevalence of obesity throughout the world and the underlying manifestations of diabetes and insulin resistance. Adipose tissue itself can give rise to cytokines that decrease insulin sensitivity, which provide a systemic pro-inflammatory stimulus [394]. The primary aim of the current diabetes management strategies is to achieve tight blood glucose level control. However, intensive blood glucose control alone does not necessary reduce the risk of developing diabetic vascular complications [14]. Therefore, there is an urgent need to understand the molecular mechanisms behind the progression of diabetic complications in order to effectively implement appropriate therapeutic measures. The findings of this review confirm the important roles of oxidative stress and inflammation as primary instigators in the pathogenesis of diabetic vascular complications. The research to date opens new opportunities in the development of novel and effective strategies to complement and even add to the current available treatments. In this review, we have explored the molecular mechanisms in diabetic vascular complications and summarized the evidence for the development of diabetic complications, which are potentially linked to oxidative stress and inflammation. We further extended the review to the molecular level by explaining the important role of cellular signalling pathways, particularly NF-κB signalling involved in diabetic vascular complications through the triggering of vascular inflammation, as well as its link to oxidative stress.

Diabetic vascular complications are postulated to be initiated and exacerbated by multiple signalling pathways which are obviously linked to each other in a synergistic order. Many researchers undertake animal and clinical studies which are mostly based on traditional records and observational documentations. Even though animal and clinical studies provide higher levels of evidences, their initiation is often restricted by cost, time and ethical issues. Therefore, *in vitro* assays are still a valuable starting point to provide supporting evidence for the commencement of higher level *in vivo* experimental studies. In order to select a suitable *in vitro* model for a disease condition, it is necessary to recognise the molecular mechanisms involved in accordance with previous observations. NF-κB is a central signalling hub implicated in inflammation and serves as a common element linking all major inflammation-related pathways. This target provides a potentially effective strategy against diabetic complications. In addition, oxidative stress scavenging properties of a particular natural preparation or compound could further accentuate the prevention of vascular disease in diabetes. As herbal medicines possess a mixture of phytochemicals, their role in targeting multiple inflammatory pathways in a synergistic manner could mean that herbal medicines may be an effective solution to the prevention and management of diabetic vascular complications. Furthermore, there may be some molecular mechanisms that overlap between different disease conditions, for example the involvement of NF-κB signalling pathway in atherosclerosis and cancer, which may lead to new therapeutic uses of a herbal preparation. As a result, understanding the molecular mechanisms involved is a relatively modern scientific approach to elucidate the potential health benefits of a herbal preparation, which requires further scientific evidence from higher levels of experimental design to support their therapeutic or preventative use.

An increasing amount of current research has been conducted to evaluate the potential benefits of herbal medicines and nutraceuticals in the prevention and treatment of diabetic complications. As shown in this review, herbal medicines and nutraceuticals have been identified which may offer potential opportunities in identifying direct vascular anti-oxidative or anti-inflammatory agents. Due

to the fact that the clinical knowledge of herbal medicine has evolved from traditional practices and there is a limited number of clinical trials, the issues of safety and efficacy of herbal medicines has become a major concern. Therefore, it is not surprising to find that a large effort has been put into researching herbal medicines and nutraceuticals *via* scientific and evidence-based approaches. Phytochemical studies at centres like our Herbal Medicine Research and Education Centre (HMREC) utilize advanced techniques (e.g. qualitative and quantitative chromatographic methods) which have provided invaluable supporting evidence in identifying various bioactive components in a particular herb or formula, thus helping to identify the molecular mechanisms of herbal medicines associated with clinical outcomes for the prevention of diabetic complications. From our understanding, the currently available ranking system for level of evidence in the field of herbal medicines and nutraceuticals does not place a high emphasis on scientific evidence from animal, cellular and chemical studies. Whilst such evidence may be considered supportive, in reality most research studies on herbal medicines and nutraceuticals are dominated by animal, cellular and chemical works, while there is limited clinical evidence available at present. This may influence current perceptions of these medicines and hence limit the future development of herbal medicines and nutraceuticals. Thus, incorporating the valuable evidence from animal, cellular and chemical studies into the existing system should be important adjunctive evidence to clinical evidence, providing a valuable approach in recognising and further developing the potential health benefits of herbal medicines and nutraceuticals.

In this review, we have provided a summary of the scientific evidence of herbal medicines, nutraceuticals and phytochemicals regarding their benefits in the management of diabetic complications from both clinical and animal studies. A series of highest level of clinical studies (i.e. well-designed, randomized and controlled clinical trials) have recently been carried out for several different pharmacological strategies for 10 natural products with promising results for the management of diabetic complications including *Capsicum frut*escens, *Centella asiatica*, fish oil, *Ginkgo biloba*, *Linum usitatissimum*, *Pinus pinaster*, *Salvia hispanica*, *Salvia miltiorrhiza*, *Tinospora cordifolia* and *Vitis vinifera*, as well as a naturally occurring phytochemical, γ-linolenic acid. At least 8 other natural products, *Astragalus membranaceus, Cinnamomum zeylanicum, Glycine max,* honey, *Juglans regia, Panax notoginseng,* propolis and *Punica granatum* have also been reported to be beneficial in the management of diabetic complications in human subjects. Interestingly, we found that at least 30 other natural products such as *Gynostemma pentaphyllum* and *Zingiber officinale*, as well as 34 other naturally occurring phytochemicals have only been evaluated in animal studies regarding their beneficial effects in diabetic complications. As a consequence, these natural products and phytochemicals are worthy of future investigations into their potential clinical usage in diabetic complications.

One focus of this review was to provide a linkage between the outcome observed from human and animal subjects for a natural product and its phytochemical content. The success of these categories of natural products in the clinical settings has prompted intense investigation on their role in vascular inflammation, to assemble a more complete picture of the mechanism(s) involved in the clinical benefit observed. Since bioactive phytochemicals are considered important in mediating the beneficial effects of a natural product in physiological conditions, analyzing the biological activities of phytochemicals is a useful way to correlate the health benefits of herbal medicines and nutraceuticals. Therefore, chemical analyses form an integrated part of the level of evidence for herbal medicines and nutraceuticals. According to our literature search, there is at least one naturally occurring phytochemical, γ-linolenic acid, that has been evaluated at the highest level of clinical evidence regarding its beneficial effects in diabetic complications, while at least 34 phytochemicals have been evaluated in animal models of diabetic complications. Since inflammation-related NF-κB signalling pathways have recently been shown to be important in the development of diabetic complications, we further summarized the literatures on phytochemicals showing positive effects against the NF-κB signalling pathway. At least 44 phytochemicals, mostly flavones and flavonols, have been evaluated regarding their activities on NF-κB and NF-κB-mediated inflammatory responses, particularly leukocyte recruitment, a crucial feature in the development of diabetic vascular complications, using cellular and animal models. The anti-oxidative activities of phytochemicals are of interest amongst health professionals and the community, thus we also summarized the anti-oxidative activities of the 44 phytochemicals and explained the potential linkages between their anti-oxidative and NF-κB suppression activities. The bioactive phytochemicals in diabetic complications occur most frequently in the chemical categories of fatty acids, lipids, alkaloids, flavones and flavonols, phenolics, and terpenoids. Interestingly, evaluation of the information gathered showed that several phytochemicals displaying positive effects against diabetic complications in animal models, and was correlated with their suppressive effects on NF-κB and leukocyte recruitment. This includes astragaloside IV, curcumin, epigallocatechin gallate, magnolol, protocatechualdehyde, quercetin, resveratrol and tanshinone IIA. The mechanisms exhibited by the phytochemicals may explain the biological activities observed in the medicinal plants.

Metabolic syndrome, also known as syndrome X, is widely accepted as a cluster of metabolic risk factors including glucose intolerance, central obesity, hypertension and dyslipidaemia [395]. Published works demonstrated that the common health concerns of metabolic syndrome is the increased risk of developing type 2 diabetes and cardiovascular disease [395-397]. Herbal medicines and nutraceuticals are of great interest due to their crucial multi-target properties. Together with the importance of anti-inflammatory effects in diabetic complications by herbal medicines and nutraceuticals, their effects on blood glucose, blood lipid and blood pressure will provide combinatory benefits, and act as a holistic approach for the management of metabolic syndrome. The herbal medicines and nutraceuticals included in this review are not necessary a comprehensive list due to the limit of scope and searching strategies. Many other natural products, exhibiting hypoglycaemic, anti-inflammatory, anti-oxidative and/or lipid-lowering activities, are also useful in metabolic syndrome, and are potentially beneficial for the prevention and treatment of diabetic complications.

In conclusion, scientific evidence demonstrates the important role of inflammation in the pathogenesis of diabetic complications, which may be explained by several molecular mechanisms, particularly the NF-κB signalling pathways. Phytochemicals occurring in many herbal medicines and nutraceuticals act through these mechanisms and provide safe and effective candidates for drug design and development of treatment for diabetic complications. At the same time, the study of the mechanisms of action and active components in herbal medicines and nutraceuticals have greatly enhanced our understanding on the rationale underpinning popular usage of some herbal medicines and nutraceuticals for the prevention and treatment of diabetic complications. Further studies are required to generate a matrix of scientific evidence at the clinical and pre-clinical levels, including chemical, cellular and animal studies, in order to develop effective medicines for the prevention and treatment of diabetic complications.

ABBREVIATIONS

AGE	=	Advance glycation end product
AP-1	=	Activated protein-1
CE	=	Capillary electrophoresis
CTGF	=	Connective tissue growth factor
eNOS	=	Endothelial nitric oxide synthase
H_2O_2	=	Hydrogen peroxide

HPLC	=	High pressure liquid chromatography
HUVEC	=	Human umbilical vein endothelial cells
ICAM	=	Intercellular adhesion molecular-1
IKK	=	IκB kinase
IL	=	Interleukin
iNOS	=	Inducible nitric oxide synthase
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen-activated protein kinases
MCP-1	=	Monocyte chemoattractant protein-1
NADPH/NADPH	=	Nicotinamide adenine dinucleotide phosphate
NF-κB	=	Nuclear factor-kappa B
NHMRC	=	Australian National Health and Medical Research Council
NO	=	Nitric oxide
•OH	=	Hydroxyl radical
$ONOO^-$	=	Peroxynitrite
O_2^-	=	Superoxide
PKC	=	Protein kinase C
PPAR	=	Peroxisome proliferator-activated receptors
RAGE	=	receptor of advanced glycation end product
ROS	=	Reactive oxygen species
TGA	=	Therapeutic Goods Administration
TGFb1	=	Transforming growth factor b1
TLC	=	Thin layer chromatography
TNF-α	=	Tumour necrosis factor-alpha
TPA	=	12-O-tetradecanoylphorbol 13-acetate
VCAM-1	=	Vascular cell adhesion molecule-1
VSMC	=	Vascular smooth muscle cells

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