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Protective role of nutraceuticals against myocarditis

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ABSTRACT

Myocarditis is an inflammatory disease of the myocardium that mostly affects young adults. The disease is commonly caused by viral infection, medications, autoimmune disorders, and inflammatory conditions. Nearly 50% of the cases of myocarditis are due to post-viral immune response in a setting of an identifiable or non-identifiable infection. The clinical manifestation is nonspecific ranging from asymptomatic courses to sudden death in infants and young patients. This review describes the properties of phytochemicals as plant-derived active ingredients which can be used in the prevention and treatment of myocarditis and its associated risk factors. Meanwhile, it has illustrated epidemiological analyses, mechanism of action, and the metabolism of phytochemicals in animal and human clinical trials. We also mentioned the precise mechanism of action by which phytochemicals elicit their anti-viral, anti-inflammatory, antioxidant, and immunomodulatory effects and how they regulate signal transduction pathways. Nevertheless, comprehensive clinical trials are required to study the properties of phytochemicals in vivo, in vitro, and in silico for a proper management of myocarditis. Our findings indicate that phytochemicals function as potent adjunctive therapeutic drugs in myocarditis and its related complications.

Abbreviations: ACE, Angiotensin-converting enzyme; AMPK, ATP-activated protein kinase; AP-1, Activator protein 1; ARBs, Angiotensin II receptor blockers; Bcl-2, B-cell lymphoma 2; BNP, Brain natriuretic peptide; BW, Body weight; CAT, Catalase; CCL2, C-C Motif Chemokine Ligand 2; CD4 + and CD8 +, T-lymphocytes subsets of spleen; cMLC1, Cardiac myosin light chain-1; COX-2, Cyclooxygenage-2; CPK, Creatine phosphate kinase; 3Cpro, 3 C protease; cTnI, Cardiac troponin I; CTX, Cyclophosphamide; CXCL1, Chemokine (C-X-C motif) ligand 1; ± dp/dtmax, Maximum changing rate of ventricular pressure; EAM, Experimental autoimmune myocarditis; ER, Endoplasmic reticulum; ET-1, Endothelin-1; EV71, enterovirus 71; FAS/FASL, Fas/Fas ligand; GPx, Glutathione peroxidase; GR, Glutathione reductase; GSH, GSSG into reduced glutathione; GST, Glutathione-S-transferase; HW, Heart weight; IFN-γ, Interferon-γ; IGF-1, Insulin-like growth factor 1; IGF-1R, Insulin-like growth factor 1 receptor; IGFBP3, Insulin like growth factor binding protein 3; iNOS, Inducible nitric oxide synthase; JNKs, c-Jun N-terminal kinases; LDH, Lactate dehydrogenase; IL, Interleukin; LVDP, Left ventricular developed pressure; LVEDP, Left ventricular end-diastolic pressure; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameters; LVFS, Left ventricular fractional shortening; MAPK, Mitogen activated protein kinases; Map1lc3, Microtubule-associated proteins 1 A/1B light chain 3B (LC3); MDA, Malondialdehyde; MIP-1α, Macrophage inflammatory proteins-1α; MMP, Matrix metalloproteinase; α7 nAChR, α7 nicotinic acetylcholine receptors; NADPH, Nicotinamide adenine dinucleotide phosphate; NF-κB, Nuclear factor-κB; NOX4, NADPH Oxidase 4; Nrf2, Nuclear factor erythroid-2-related factor-2; NSP2, Nonstructural protein 2; NTR, Non-translated region; OPN, Osteopontin; PARP, Poly ADP ribose polymerase; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PTnI, Plasma troponin I; ROS, Reactive oxygen species; SDHA, Succinate dehydrogenase complex flavoprotein subunit A; SERCA2, Sarco/endoplasmic reticulum Ca^{2+}-ATPase 2; SOD, Superoxide dismutase; SMAD7, SMAD family member 7; STAT, Signal transducer and activator of transcription; TFEB, Transcription Factor EB; TIMP-1, Tissue inhibitor of metalloproteinase-1; Th 1/2, T helper 1/2; TL1A, TNF-like ligand 1 aberrance; TNF-α, Tumor necrosis factor; TRAP1, Tumor necrosis factor receptor associated protein 1; UCP2, Uncoupling Protein 2; VDR, Vitamin D receptor; Vps11, Vacuolar protein sorting-associated protein 11.

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1. Introduction

Myocarditis, an inflammatory disease of the myocardium, is categorized into three main groups including post-viral autoimmune-related, autoimmune-mediated (lupus myocarditis, giant-cell myocarditis) and drug-associated (hypersensitivity myocarditis, toxic myocarditis) [6–8]. However, more than 50% of the cases of myocarditis are post-viral immune-related in the setting of an identifiable or non-identifiable infection (Fig. 1) [4,9]. Patients are commonly asymptomatic or present with nonspecific symptoms including fever, fatigue and arthralgia. Some also experience dyspnea or cardiac signs from angina and arrhythmia to heart failure, dilated cardiomyopathy or sudden death [1–3]. The annual prevalence is estimated to be nearly 17 per 100, 000 population worldwide and less than 2% of mortalities occur in infants and young adults due to sudden cardiac death [5]. The diagnosis of myocarditis cannot be made by myocardium inflammation alone since many diseases such as myocardial infarction can also cause secondary inflammation [1]. The main inflammatory cells that infiltrate the heart during myocarditis are T-lymphocytes,macrophages and NK cells (Fig. 2) [1,10]. The initial management of myocarditis is treatment of the underlying diseases but cardiac symptoms require additional medications such as digoxin, diuretics, ACE inhibitors, ARBs, beta blockers and corticosteroids. Nevertheless, effective treatment strategies for myocarditis are still limited [11]. Recently, natural compounds and herbal medicines are found to exert protective effects against mortality in viral myocarditis [12]. Phytochemical have been traditionally used in the treatment of various diseases including cardiovascular disorders [2, 13]. In this review, we have highlighted phytochemicals with protective effects against myocarditis based on traditional and conventional medical reports.

2. Phytochemicals: classification and benefits on myocarditis

Preclinical and clinical researches have documented the protective effects of natural products in prevention and treatment of myocarditis. Chemical structures of these products are illustrated in Fig. 3. The main phytochemicals derived from common medicinal plants are discussed below.

2.1. Polysaccharides

Polysaccharides (mucilages and pectin), derived from medicinal plants such as *Althaea officinalis* L., sweet potato, and grapefruit, are macromolecules with various biological activities including antioxidant, antitussive, antiviral, immunostimulatory, anti-inflammatory, anti-tumor, and cardioprotective [14–17]. Polysaccharides suppress apoptosis and activation of STAT pathway along with TLR-induced TNF expression associated with viral replication and inflammation. They particularly exert cardioprotective effects through their antioxidant, anti-inflammatory and immune-modulatory properties [18]. Pectin inhibits inflammation through regulation of AMPK, Nrf2, and NF-κB signaling pathways. It also functions as a potential prebiotic which protects against cardiovascular diseases via modulating the activity of GST, GSH, GR, GPx, and GSSG as well as increasing CAT and decreasing pro-inflammatory cytokines [15,18]. Additionally, polysaccharides exert immunomodulatory activities by enhancing organ index, macrophage phagocytosis, NK cell activity, the percentage of $CD4^+$ and $CD8^+$ T cells, the ratio of $CD4^+/CD8^+$,T cell and B cell proliferation and regenerating IL-2, IL-6, TNF-α, IL-8, IL-10 and IFN-γ in CTX-induced immunosuppressed mice models [19]. Hence, polysaccharides exhibit anti-myocarditis effects through their antioxidant, anti-inflammation and immunomodulatory properties.

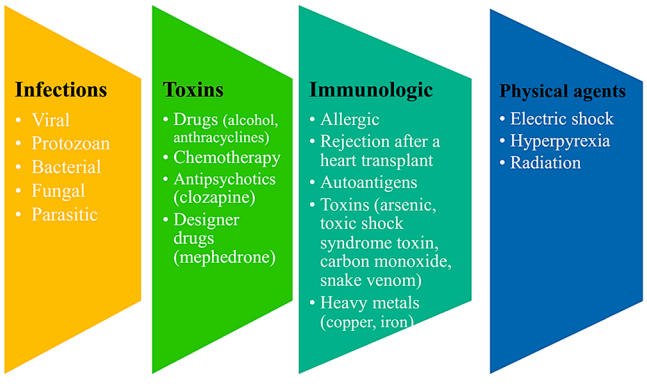

Fig. 1. Direct potential causes of myocarditis.

2.2. Polyphenols and simple phenols

Polyphenols are a large group of phytochemicals and plant-based foods including fruits, vegetables, cereals and beverages with more than one phenolic groups [20,21]. Natural polyphenols possess cardioprotective properties due to their antioxidant, anti-inflammatory, immunomodulatory and cardio-protective activities [22]. Apples absorb into the bloodstream due to their rich phenolic content and exert their beneficial effects [23,24]. Flavonoids in apple leaves (hyperoside, isoquercitrin, avicularin, rutin, and quercitrin), dihydrochalcones (phloridzin, and phloretin), phenolic acids and flavon-3-ols (catechins and epicatechin) have revealed a high antioxidant activity with a DPPH < ABTS < FRAP pattern. Flavanols including epicatechin, catechin and oligomeric flavan-3-ols (procyanidin B1 and B2) are also found in apple fruits [22]. Apple flavanols are shown to reduce inflammation via inhibiting transcription factor NF-κB and the expression of NF-κB-regulated genes as well as their immunomodulating activity [23]. Chlorogenic acid, a phenolic acid in apple, is potent free radical scavenger. Generally, flavonoids and phenolic ingredients in apple are shown to decrease cardiovascular incidents through antioxidant activities, up-regulation of lipoprotein lipase activity and anti-inflammatory properties [24]. Moreover, apple polyphenols increase antioxidant/anti-inflammatory defense by reducing the expression of pro-inflammatory cytokines, COX-2 inhibition, down-regulation of NF-κB, TNF-α, IL-1β, IL-6 and IL-8, inhibiting ROS which generates and

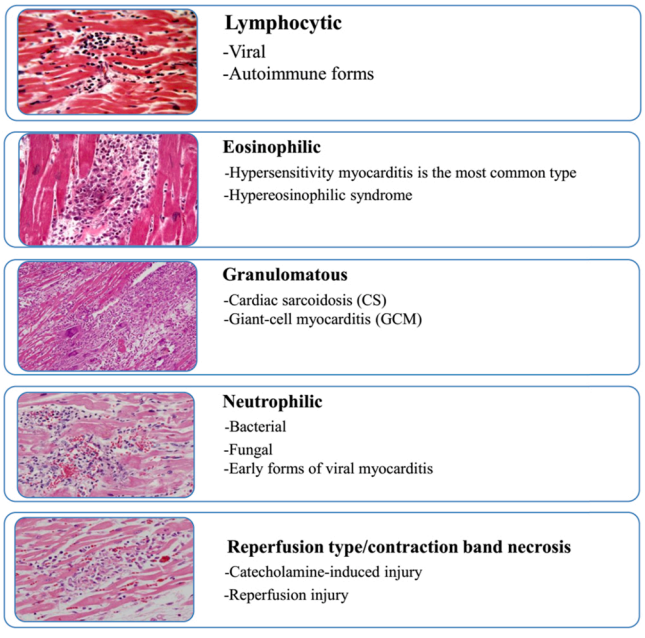

Fig. 2. Microscopic findings of the histologic patterns of myocarditis and inflammatory cardiomyopathy [55].

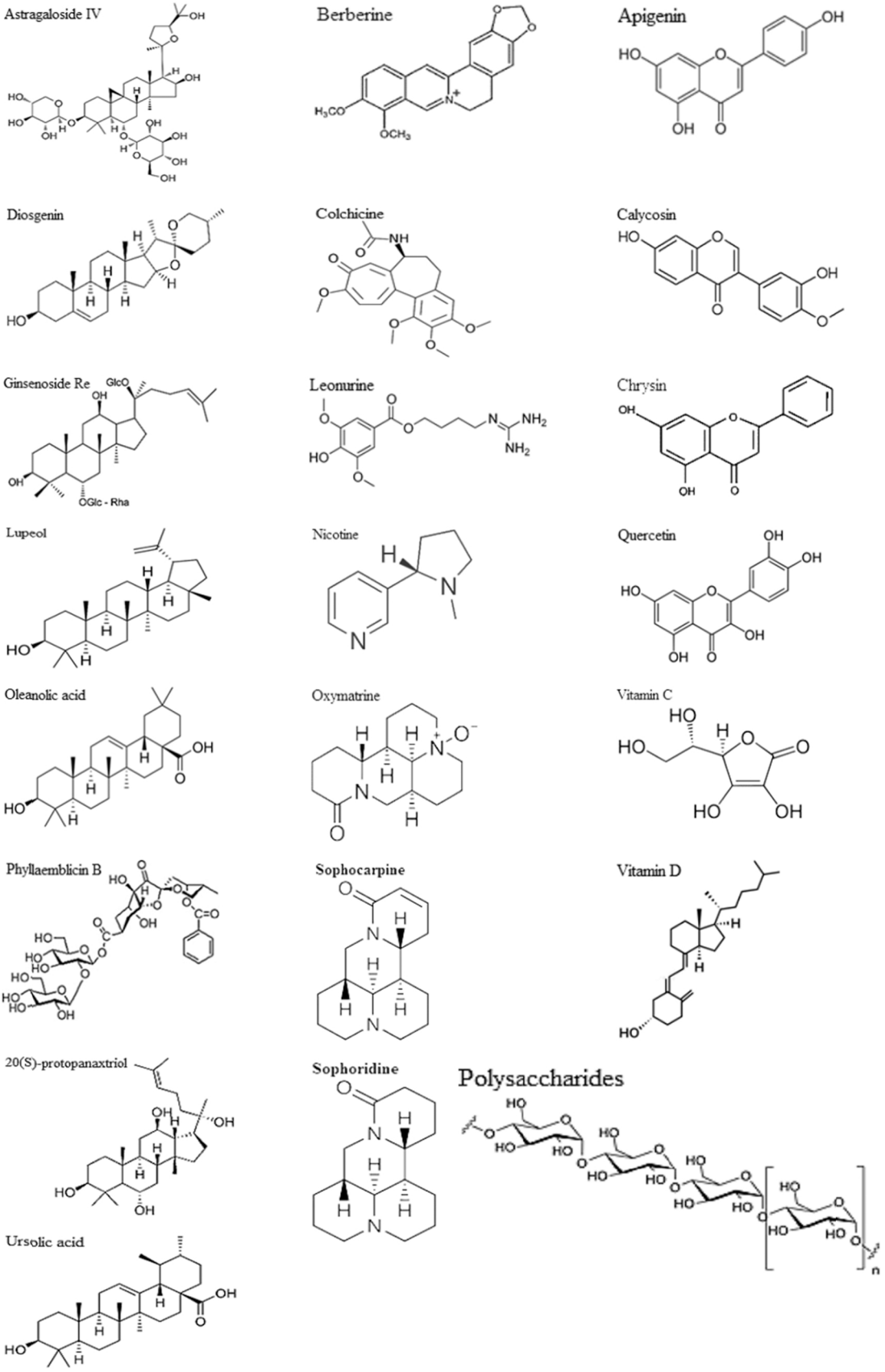

Fig. 3. Chemical structures of natural products with anti-myocarditis activities.

upregulates the expression of Nrf2 and PGC-1a [24], increasing NO and eNOS and decreasing iNOS [25]. Additionally, grape seeds contain phenols such as proanthocyanidins which could prevent cisplatin-induced cardiotoxicity in rats through reducing LDH, ALT, ALT, MDA and CK along with increasing GSH, GSH-Px, SOD and NO [26]. Polyphenols are shown to attenuate doxorubicin-induced cardiomyocyte toxicity by decreasing ROS generation; they also increase doxorubicin antitumor activity through enhancing lymphocyte proliferation, NK cell cytotoxicity, CD4 + /CD8 + ratio, and production of IL-2 and IFN-γ. The proanthocyanidins possess cardioprotective properties since they modulate NO/cyclic GMP pathway, function as ROS scavengers, induce vasodilation, abrogate lipid peroxidation, and inhibit inflammatory markers such as IL-1β, p38 MAPK, NF-κB and JNK. These polyphenols also exert immunomodulatory effects by reducing inflammatory cells, cytokines secreted by Th2 cells, ROS and MMP levels, serum IgE levels and modulating NF-κB [27]. Notably, proanthocyanidins can abolish replication of respiratory syncytial virus (RSV) by inhibiting phosphorylation of NF-κB, ERK, p38, AP-1 and MAPK/JNK [28]. Consequently, proanthocyanidin could protect against myocardial damage and exert anti-myocarditis effects via their antioxidant, anti-inflammatory and immunomodulatory properties. It has been reported that some natural polyphenolic compounds (e.g. apigenin and quercetin flavonoids, curcumin, chlorogenic acid, resveratrol, catechin, gallocatechin, epicatechin and epigallocatechin) can alleviate autoimmune myocarditis via upregulation of Th1/Th2 cytokine balance, modification enzymes involved in oxidative stress, modulation of mitogen-activated protein kinase signaling pathway and increasing SERCA2 levels [2].

2.2.1. Apigenin

It is previously reported that apigenin and quercetin have a flavonoid structure and they can exert anti-myocarditis activities via modulating Th1/Th2 cytokine balance, elevating Ca^{2+}-ATPase levels and alleviating the severity of EAM in myocarditis [2,29]. Also, apigenin was found to reduce LPS-induced expression of pro-inflammatory cytokines including TNF-α, IL-1β, MIP-1α, MIP-2, NFκB; it also ameliorated antioxidant enzymes and redox balance against oxidative stress and inflammatory response [30].

2.2.2. Quercetin

The immunomodulatory and anti-inflammatory effects of quercetin are due to antioxidant properties, modulation of MAPK signaling pathway, production of IL-10, inhibition of myocardial endothelin-1, TNF-α, IL-12, IL-17 and Th1 differentiation [2,31–33]. Furthermore, treatment of myocarditis with quercetin has been associated with elevated numbers of T regulatory cells and anti-inflammatory cytokines and reduced secretion of pro-inflammatory and myocardial apoptosis [31,32,34].

2.2.3. Chrysin

Chrysin (5,7-dihydroxyflavone) is a flavone extracted from various plants (including *Passiflora incarnate* L. and *Passiflora caerulea* L.), mushrooms, honey or propolis which functions as an antioxidant, anti-inflammatory and anti-apoptotic agent [35,36]. Chrysin and especially its substituted benzyl derivatives have shown significant anti-viral activities and suppressed CVB3 infection-induced viral myocarditis in mice through blocking IκBα/NF-κB signaling pathway mediated CXCL1 transcription and inhibiting viral protein cleavage [35]. Moreover, chrysin may modulate inflammatory responses involved in cardiovascular disorders (CVDs) via suppressing JNK and NF-κB signaling pathways, diminishing IκB kinase (IKK) complex-induced transcription activation, blocking IkBα phosphorylating and NF-κB activation [36]. Additionally, 38 active ingredients with different flavonoid structures (flavanols, flavones, flavanones, flavanols, and isoflavones) including icariin, salvianolic acid B, and plantainoside D, are found to inhibit IKKβ which could contribute to their cardioprotective potential in inflammatory response associated with CVDs [36]. Consequently, flavonoids which are IKKβ inhibitors could suppress inflammation, chemokines, adhesion molecules and myocardial fibrosis in myocarditis. (Table 1).

2.2.4. Calycosin

A recent study highlighted that total flavonoids found in *Astragalus* (e.g. Apigenin, Luteolin, Salvigenin, Sorbifolin, Kaempferol, Quercetin, Fisetin, Naringenin, Phloretin, Sulfuretin, Genistein, Daidzein, Calycosin, Astragaluquinon, Vitexin) possess a therapeutic potential in coxsackievirus B3 (CVB3) infection-induced myocarditis [37]. They promote calumenin mRNA and protein levels and its association with SERCA2, and regulate calcium homeostasis and ER stress in cardiomyocytes resulting in improved pathogen-induced cardiomyopathy. Also, Astragalus flavonoids reduced CVB3 replication in a mouse model of myocarditis via enhancing the expression of ER chaperone proteins, inhibiting unfolded viral protein extension in ER and restoring transcriptional program to a pro-resolving profile [38]. Calycosin and its glucosides are the most abundant flavonoids in Astragali Radix and other Astragalus species. They are known for their immune-enhancing, anti-inflammatory, antioxidant, and cardioprotective properties in CVDs and autoimmune myocarditis reported in some in vitro and in vivo studies [39]. Therefore, bioactive phenolic phytochemicals found in plant foods and dairy products can employ favorable biological responses through their antioxidant, anti-inflammatory and immune-enhancing effects. They effectively modulate specific molecular pathways which include increasing AMPK phosphorylation, PKA activation, NO release, vasodilation and eNOS activation, as well as decreasing TLR4 expression, NFκB activation, apoptosis, inflammatory cell infiltration, ROS production, ERK1/2 phosphorylation, P38MAPK phosphorylation and vascular ion channels modulation [40,41].

2.3. Alkaloids

Alkaloids are a major natural phytochemical group that could prevent oxidative stress, inflammation, arrhythmia, platelet aggregation, myocardial–cerebral ischemia/reperfusion injury and autoimmune disorders [42,43]. Some studies have indicated that anti-myocarditis effects of natural alkaloids and alkaloid-contained medicinal plants are implemented through regulating cytokine expression, activation or suppression of specific kinases and signaling pathways, antioxidant and anti-inflammation effects, improving cardiac dysfunction, minimizing viral replication, and enhancing autoimmunity [44–48].

2.3.1. Sophoridine

Sophora flavescens Ait. (*S. flavescens*) alkaloid has showed antiviral effects in mice by regulating the expression of cytokines, decreasing viral load and provoking the expression of IL-1 and IFN-γ and TNF-α inhibition [47].

2.3.2. Sophocarpine

A quinolizidine alkaloid of *S. flavescens* root has exhibited markedly dose-dependent reduction in viral myocarditis via suppressing viral replication, improving cardiac function and decreasing arrhythmia in in-vitro, in-vivo and clinical studies [48].

Oxymatrine is another alkaloid of *S. flavescens* with vital bioactivities including anti-inflammation, antitumor, immunomodulation, anti-proliferative effects which also protects against angina pectoris, atherosclerosis, myocardial infarction (MI), and stroke. It exerted protective effects against coxsackievirus B3-induced myocarditis in BALB/c mice through decreasing CVB3 titer, LDH, CM-CK, and TNF-α,and regulating NTR and IFN-γ gene expression both in vitro and in vivo [49].

Berberine, an alkaloid isolated from traditional herbal medicines (*Hydrastis canadensis, Cortex phellodendri*, *Berberis* and *Coptis*), has significant anti-viral, immunostimulatory, cardioprotective, anti-inflammatory and antioxidant properties [44,45,50]. Berberine

Table 1
Protective effects of phytochemicals on myocarditis.

Phytochemical classification	Phytochemicals	Molecular formula	Dose and treatment period	Model	Protective effect	Mechanism	Ref.
Polysaccharides	Polysaccharides	–	50,100,150 mg/Kg/ BW/daily gavages for 9 days	mice	antioxidant, antitussive, antiviral, immunostimulatory, anti-inflammatory	↑STAT pathway, GST, GSH, GR, GPx, GSSG, CAT, AMPK, Nrf2, $CD4^{+}$/ $CD8^{+}$, IL-2, TNF-α, IFN-γ	[19]
Polyphenols and simple phenols	Apigenin	$C_{15}H_{10}O_5$	20, 100, 200 mg/kg/ day orally for 21 days 50 mg/kg (IP)	BALB/c mice Male C57BL/ 6 mice	antioxidant, immunostimulatory, anti-inflammatory, modulate autophagy	↑Cardiac function, IL-4, IL-10, Th2, TFEB, Ca^{2+}-ATPase ↓IFN-γ, TNF-α, IL-2, Th1, LDH, CK, cMLC1, cTnI, PARP, apoptosis, necrosis, MIP-1α, MIP-2, Vps11, Map1lc3	[29,30]
	Calycosin	$C_{16}H_{12}O_5$	5, 20,50 mg/kg/day (IP) for 7 days	Mouse HL-1	Immunomodulatory, anti-inflammatory, antioxidant, cardioprotective, anti-viral	↓Viral replication, ↑Calumenin protein, mRNA expression, cardiac function, SERCA2	[38,39]
	Chrysin	$C_{15}H_{10}O_4$	0.4, 2, 10, 50 μM (IP) for 5 days and 48 h	Inbred BALB/c mice Vero cells	antioxidant, anti-inflammatory, anti-apoptotic, anti-viral	↓IκBα/NF-κB, viral replication, CXCL1, viral 3 C^{pro}, EV71, JNK, IκB, IκBα, IKKβ	[35,36]
	Quercetin	$C_{15}H_{10}O_7$	10 or 20 mg/kg orally for 21 days 10 mg/kg for 28 days	Dark Agouti (DA) rat Rat	antioxidant, anti-inflammatory, anti-apoptotic, anti-viral, immunomodulatory	↑IL-10, protection against the adverse cardiac remodeling ↓TNF-α IL-12, IL-17, EAM, Th1, ER, ET-1/p38 MAPK/Akt, $p67^{phox}$, infiltration, GRP78, GADD153, cytosolic cytochrome C, TGF-β1, OPN, ERK1/2	[31–33]
Alkaloids	Berberine	$C_{20}H_{18}NO_4^{+}$	200 mg/kg/day orally for 21 days (2.5,5,10,25,50,100) μM treatment for 20 h 100 mg/kg/day	Rat HeLa cells Rat	anti-viral, immunostimulant, cardioprotection, anti-inflammatory, antioxidant	↓Viral replication, VP1, JNK/p38 MAPK, NF-κB, Th17/Th1, ROS, NADPH, AP-1, PPARα, fibrosis, infiltration, ↑JAK-STAT, IL-17, IFN-γ, LVEDD, LVESD, LVEF, LVFS, PI3K/Akt/ eNOS, Nrf2, SOD, UCP2, AMPK	[44,45, 50]
	Colchicine	$C_{22}H_{25}NO_6$	1 mg once daily for 30 days 2 × 0.5 mg twice daily for 2 years	Clinical (RCT) A case report (non-RCT)	anti-inflammatory, anti-fibrotic, anti-viral, immunity	↓Inflammation, fibrotic, mitosis, microtubule assembly, viral replication, deposition kappa (κ), lambda (λ) light-chain protein ↑Cardiac function, overall survival	[51,54]
	Leonurine	$C_{14}H_{21}N_3O_5$	15, 30 mg/kg (IP) 0.5 h prior to LPS intervention 15 mg/kg/day intragastric for 8 weeks 5–20 μM treatment for 4 h	C57BL/6 mice Rat H9c2	anti-inflammatory, anti-viral, immunity, antioxidant	↓p-iκBα, p-p65, NF-κB, infiltration, MCP-1, IL-1β, IL-6, TNF-α, NOX4, MDA, Caspase 3, Caspase 9, Bax, ROS ↑Cardiac function (EF, FS, ESV, EDV, LVIDs, LVIDd), SOD2	[65–71]
	Nicotine	$C_{10}H_{14}N_2$	0.4 mg/kg three times per day (IP) for 14 days 0.1, 0.2 or 0.4 mg/kg three times per day (IP) for 7 or 14 days 7 mg overnight transcutaneous 0.1–100 μmol/L	BALB/c mice Male BALB/c mice In vivo human responses to endotoxin Human monocytes	Anti-inflammatory, Immunomodulatory	↓IL-1β, IL-6, IL-17A, TNF-α, CCL2, IL-8, IL-10, CXCR4, IRF4, CD14, ICAM-1, CD40, NF-κB, ↑TGF-β1, IL-4, CCR2, CXCR6, IL-1α, α7 nAChR, cardiac function	[55–58]
	Oxymatrine	$C_{15}H_{24}N_2O_2$	20 mg for 5 or 12 days	BALB/c mice	anti-inflammatory, antitumor, antiviral, immunomodulatory, antiproliferative	↓CVB3 titer, LDH, CM-CK, TNF-α, NTR, IFN-γ	[49]
	Sophocarpine	$C_{15}H_{22}N_2O$	7.5, 15, or 30 mg/kg/ twice daily (IV) for 14 days 10, 20, 40 mg/kg, gavage for 6 weeks	Beagle dogs Rat	anti-inflammatory, antitumor, antiviral,	↓Viral replication, arrhythmia, IL-6, IL-1β, MMP-2, MMP-9, Collagen, p-iκBα, NF-κB ↑cardiac function (LVEDP, LVSP	[48,96]
	Sophoridine	$C_{15}H_{24}N_2O$	20 or 40 mg/kg daily orally for 7 days 1 or 5 μg/ml incubated 72 h	BALB/c male mice Rat neonatal myocardial cells	anti-inflammatory, antitumor, antiviral	↑IL-1 and IFN-γ ↓TNF-α, viral titer, HW/BW, necrosis, infiltration,	[47,97]
Terpenoids	Astragaloside IV	$C_{41}H_{68}O_{14}$	100 mg/kg daily gavage for 2 weeks 20 or 40 mg/kg daily gavage for 10 days 10 μM, for 24 h	C57BL/6 mice BALB/c mice Cardiac	Antioxidant, anti-inflammatory, Immunomodulatory, antiviral, anti-fibrotic, anti-apoptotic	↑Cardiac function, MMP13, MMP14, A20 (TNFAIP3), SOD, CAT, GSH, IFN-γ, Bcl2, TIMP-1, Smad7 ↓TGF-β1, pSmad2/3, Smad4, TNF-	[73–75, 77–78, 80]

(*continued on next page*)

Table 1 (*continued*)

Phytochemical classification	Phytochemicals	Molecular formula	Dose and treatment period	Model	Protective effect	Mechanism	Ref.
			300 mg/L in drinking water	myocytes BALB/c mice		α, IL-1β, IL-6, IKKβ, IκBα, p65, NF-κB, MCP-1, $CD3^+$, $CD11b^+$, Ca^{2+}/CaN, LDH, CK-MB, CTnI, ROS, MPO, MDA, virus replication, caspase 3, caspase 8, FAS/FASL, IGF-1, IGF-1R, IGFBP3, Bax, TLR4/P38MAPK/MCP-1	
	Diosgenin	$C_{27}H_{42}O_3$	50 or 100 mg/kg gavage for 4 weeks	Rat	Antioxidant, anti-inflammatory, antiviral, anti-fibrotic, anti-apoptotic	↑Cardiac function, LVDP, ± dp/dt_{max}, ↓IKK-β, NF-κB, IκB, ROS, caspase-3, DNA binding, p38-MAPK and JNK, LVEDP, CK-MB, CTnI, IL-1β, MPO	[87,98]
	Ginsenoside Re	$C_{48}H_{82}O_{18}$	8, 16, 32 mg/kg gavage for 7 days	Rat	Antioxidant, anti-inflammatory, antiviral, anti-fibrotic, anti-apoptotic	↑Cardiac function, LVDP, ↓IKK-β, NF-κB p65, IκB, MPO, CD40, IL-1β, IL-6, TNF-α,	[87,99,100]
	Lupeol	$C_{30}H_{50}O$	50 or 100 mg/kg daily (IP) for 21 days	BALB/C mice	Antioxidant, anti-inflammatory, antiviral, anti-fibrotic	↑Cardiac function (LVEDP, LVSP, HR, ↓IL-1β, COX2, TNF-α, TLR4/MyD88/NF-κB, CK-MB, CTnI, COX2,	[83]
	Oleanolic acid	$C_{30}H_{48}O_3$	50 mg/kg/day (IP) for 21 or 65 days	BALB/c mice	Antioxidant, anti-inflammatory, anti-apoptosis, immunoregulatory	↑Cardiac function, IL-10, NO, Nrf2, SOD, CAT, Treg (CD4 +CD25 +FoxP3 +) ↓CK-MB, BNP, HW/BW, ROS, IL-17A, IL-6, TNFα	[2,84,85]
	Phyllaemblicin B	$C_{33}H_{44}O_{19}$	4, 8, 12 mg/kg/day (IP) for 7 days	BALB/c mice	Antioxidant, anti-inflammatory, anti-apoptosis, antiviral	↑Bcl2, TRAP1, SDHA, GPX1 ↓LDH, CK-MB, CVB3 titer, caspase-3, necrosis, cell infiltration	[88,89]
	20(S)-protopanaxtriol	$C_{30}H_{52}O_4$	100, 200, 400 mg/kg/day orally for 7 days	HeLa cells BALB/c mice	Antioxidant, anti-inflammatory, anti-apoptosis, antiviral	↑Cardiac function ↓Virus titers, LDH, CK-MB, caspase-3, necrosis, cell infiltration	[81]
	Ursolic acid	$C_{30}H_{48}O_3$	20, 40 mg/kg/day orally for 2 days 10, 20, 30, 40 μM for 24 h 0.125,0.25, 0.5, 1, 2 mg/L for 24 h	ICR mice MA104 cells BCC-1/KMC cells	Antioxidative, antiproliferative, antiviral, immunity, anti-inflammation, anti-apoptosis	↑Cardiac function, Mcl-1, +dP/dt, −dP/dt, GSH/GSSG, Bcl2, SOD, CAT ↓Caspase 9, caspase 3, PTnI, PERK-eIF2α-CHOP, LDH, cytochrome c, PARP, ROS, MDA, Puma, Th1, TNFα, NF-κB, IκB, p65, Bax, virus titers, viroplasm size, VP6, NSP2, viral replication,	[85,86,101,102]
Vitamins	Vitamin C	$C_6H_8O_6$	100–250 mg/kg (IV)	Child (non-RCT)	anti-oxidant, anti-inflammatory, immunomodulatory	↓LDH, AST, CK, CK-MB, CD8, CTnI, ROS ↑CD4, CD3, CD4/CD8	[93]
	Vitamin D	$C_{27}H_{44}O_3$	1000 ng/kg/day (IP) for 21 days	BALB/c mice $VDR^{-/-}$ mice $Rag2^{-/-}$mice	anti-inflammatory, anti-oxidant, anti-apoptotic, immunity, autophagy modulation	↓IL-4, Th2, HW/BW, apoptosis, caspase 3, beclin1, LC3, p62, LVED, ↑VDR, $CD4^+$, IFN-γ, cardiac function, inflammatory infiltration, LVEF, LVFS	[91,92]

suppressed CVB3 replication in viral myocarditis by blocking viral capsid VP1 protein expression and JNK/p38 MAPK activation in HeLa cells and primary rat myocardial cells [45]. It also ameliorated autoimmunity in Lewis rats with myosin-induced myocarditis due to activation of JAK-STAT pathway, up-regulation of IL-17 and IFN-γ, suppression of Th17/Th1 differentiation, improving cardiac function (i.e. LVEDD, LVESD, LVEF, LVFS), and reduction of inflammation and fibrosis following autoimmune myocarditis [2,44]. Some in-vitro studies have demonstrated that berberine provokes PI3K/Akt/eNOS signaling pathway which results in TNF-*α*–induced endothelial progenitor cells' dysfunction. On the other hand, berberine exhibits its antioxidant effects by activating Nrf2 pathway, ROS inhibition, up-regulation of SOD and UCP2 and down-regulation of NADPH oxidase expression. Anti-inflammatory effects of berberine has been established by blocking MAPK and NF-*κ*B signaling pathways, attenuating transcription activity of AP-1, and PPAR*α* activation [50]. Furthermore, berberine protected against CVDs (e.g. ischemia/reperfusion, arrhythmia, hypertension, and atherosclerosis) via its negative inotropic and chronotropic activities, anti-apoptotic effect mediated by activation of AMPK, PI3K/Akt and eNOS signaling, antioxidant and anti-inflammatory properties [50].

Colchicine is a phenethylisoquinoline alkaloid derived from *Autumn crocus* and *Colchicum autumnale* with anti-inflammatory, anti-gout and anti-fibrotic effects [51–53]. It has been used in the treatment of auto-inflammatory diseases, recurrent pericarditis, viral infections and chronic active hepatitis [51]. Low dose colchicine in patients with severe viral myocarditis reduced symptoms, enhanced ejection fraction and improved clinical status in a two-year follow up period [51]. It seems that colchicine suppresses inflammation and fibrosis through binding to β-tubulin, blocking mitosis and microtubule assembly, activating β-amyloid, preventing deposition of kappa (κ) and lambda (λ) light-chain proteins, induction of apoptosis in virus cells, and inhibiting inflammasome and proinflammatory cytokines [51,54].

Nicotine is a pyridine alkaloid of *Nicotiana tabacum* plant which protects against viral myocarditis and acts as an anti-inflammatory agent in animal models [55,56]. These functions are likely due to improving left ventricular function, downregulation of inflammatory cytokines (i.e. IL-1β, IL-6, IL-17A, TNF-α, CCL2, IL-8, IL-10, CXCR4, IRF4, CD14, ICAM-1, CD40), inhibiting NF-*κ*B signaling pathways,

stimulation of α7 nAChR as an nAChRs receptor agonist, altering the expression of genes involved in immune responses, upregulation of TGF-β1, IL-4, CCR2, CXCR6, IL-1α, and alleviation of abnormal activation of microglia [55–62]. Thus, nicotine and alpha7 nAChR agonists could be promising candidates to treat viral myocarditis.

Papaver pseudocanescens alkaloids (Benzylisoquinoline, isoquinoline, isopavine, and promorphinane type) possess antiviral properties through suppressing the replication of poliovirus 1 and human rhinovirus 14. Some alkaloids of Papaveraceae family inhibit replication of influenza virus, poliovirus, encephalomyocarditis virus, herpes simplex virus, human adenovirus 5 and 12. In addition, aporphine alkaloids inhibit replication of poliovirus 1 and herpes simplex virus type 1 [63].

Leonurine Leonurine is a phenolic pseudoalkaloid derived from different plants of Lamiaceae family (e.g. *Leonotis leonurus*, *Leonotis nepetifolia*, *Leonotis artemisia*, *Leonurus cardiaca* (Motherwort), *Leonurus sibiricus)* [64]. It has substantial cardioprotective effects such as anti-atherosclerotic, anti-myocardial fibrosis, and anti-ischemic alongside improving immunity [65–69]. Also, some animal studies have proven anti-inflammatory and antioxidative effects of Leonurine in acute inflammatory diseases [70,71]. Furthermore, Leonurine attenuated LPS-induced myocarditis via regulating NF-κB signaling pathway, improving cardiac function (including EF, FS, ESV, EDV, LVIDs and LVIDd), reducing the expression of MCP-1 and proinflammatory cytokines (IL-1β, IL-6, TNF-α, p-p65 and p-IκBα), diminishing oxidative stress response (increasing SOD2 protein expression, decreasing NOX4 expression and MDA levels), downregulating the expression of Caspase 3, Caspase 9 and Bax protein and blocking myocardial apoptosis in all Leonurine doses both in vivo and in vitro [65]. Consequently, Leonurine is a new pharmacological treatment for acute inflammatory myocarditis which attenuates inflammation, oxidative injury, apoptosis and also improves immune responses.

2.4. Terpenoids

They have a complex structure and multiple therapeutic effects including hypoglycemia, neuroprotection, antitumor, anti-inflammatory, antimicrobial, antioxidant and antiaging effects. They regulate immune responses, promote transdermal absorption, prevent and treat cardiovascular disorders. Thus, terpenoids could increase the variety of drugs used in future pharmaceutical studies [72].

Astragaloside IV is a pentacyclic triterpenoid of *Astragalus* spp. (root) with anti-inflammatory, antioxidant and immunomodulatory effects. It also improves cardiac function, functions as an anti-arrhythmic, reduces myocardial viral titers and myocardial necrosis and protects against myocarditis [73]. Astragaloside IV is shown to mitigate CVB3-induced myocardial fibrosis and dilated cardiomyopathy by downregulation of TGF-β1, pSmad2/3, and Smad4 signaling pathways. Also, it improved cardiac function in inbred male BALB/c mice, upregulated the expression of MMP13 and MMP14,and is found to have anti-apoptotic and anti-fibrotic effects [73–75]. In viral myocarditis, pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IKKβ, IκBα, p65, NF-κB and MCP-1 were reduced by Astragaloside IV due to upregulation of A20 (TNFAIP3). Other anti-myocarditis effects by Astragaloside IV are mediated through decreasing $CD3^+$ and $CD11b^+$ cells and inhibiting Ca^{2+}/CaN signaling pathway [76]. Previous studies have reported that astragaloside IV reduced LDH, CK-MB and CTnI levels and improved cardiac function in animal models of viral myocarditis through increasing SOD, CAT, GSH, reducing fibrosis, virus replication, caspase 3 and caspase 8 cleavage, decreasing ROS, MPO and MDA levels, inactivation of FAS/FASL signaling pathway, inhibiting IGF-1, IGF-1R and IGFBP3, and preventing inflammation through modulating TLR4/P38MAPK/MCP-1 and NF-κB signaling pathways [77–80]. These collective results indicate that astragaloside IV exerts cardioprotective effects on viral myocarditis via prevention or activation of multiple signaling pathways, reducing heart remodeling and anti-viral, antioxidant, anti-inflammatory, anti-apoptosis and anti-fibrosis properties.

20(S)-protopanaxtriol is a main triterpene constituent of *Panax pseudoginseng* root with therapeutic effect against CVB3-induced myocarditis in HeLa cells and BALB/c mice. Its anti-myocarditis effects are due to inhibition of CVB3 replication, decreasing LDH and CK-MB levels, direct anti-inflammatory activity and anti-apoptotic properties [81].

Ginkgo biloba extract and its ingredients such as bilobalide and ginkgolide diterepenoids inhibited rat myocardial remodeling via reducing myocardial fibrosis, S100A4, MMP-3, MMP-2, MMP-9, CK-MB and type 1 collagen in BALB/c mice with myocarditis [82].

Ursane, Olean and Lupan are three major pentacyclic triterpenoids found in fruits, vegetables and many medicinal plants with numerous pharmacological functions including antioxidant, anti-inflammatory, anti-cancer, immunomodulatory and cardioprotective effects [83–85].

Lupeol was found to alleviate CVB3-induced viral myocarditis and exerted cardioprotective effects in mice by downregulation of IL-1β, COX2, TNF-α, and TLR4/MyD88/NF-κB signaling pathway [83].

Oleanolic acid can prevent myocarditis due to its antioxidant, anti-inflammatory, anti-apoptosis and immunoregulatory properties. It reduced cardiac damage markers (CK-MB, BNP) following myocarditis in both in vitro and in vivo studies [2,84,85].

Ursolic acid, a ursane type triterpene isolated from apple peel and other medicinal plants, have demonstrated beneficial effects such as potent antioxidative and antiproliferative activities [85]. It exerts cardioprotective effects by inhibiting myocardial apoptosis, modulating apoptosis and oxidation in endoplasmic reticulum (ER), dampening myocardial damage, stimulating inactivate CHOP-induced Puma, balancing intracellular redox state and pro-apoptotic proteins [85]. The efficiency of Ursolic acid in myocarditis is due to its immunomodulatory and anti-inflammatory properties, blocking oxidative stress,and suppressing Th1 responses and pro-apoptotic proteins [23,85,86].

Diosgenin and Ginsenoside Re are triterpenoid structures with promising IKK-β inhibitory roles which can also serve as novel cardioprotective agents through inhibition of NF-κB signaling pathway by IκB phosphorylation, suppressing DNA binding and p65 translocation, reducing serum levels of cardiotoxicity markers, ROS, and caspase-3 inactivation [87]. In addition, other terpenoids including Triptolide, Artemisinin, Paeoniforin, Picroside II, and Ginkgolide C can attenuate inflammatory CVDs by suppressing NF-κB cascade through inhibiting IKK-β activity [87].

Phyllaemblicin B, the main sesquiterpenoid glycoside of *Phyllanthus emblica* roots, reduced CVB3-iduced apoptosis both in vitro and in vivo. In CVB3 myocarditis mouse models, phyllaemblicin B decreased CVB3 titers, LDH and CK-MB levels, and pathological damage of myocardium [44,88,89]. Overall, all different types of terpenes have pointed out potential cardiovascular effects suggesting their potential role in designing more effective anti-myocarditis agents.

2.5. Vitamins

They are a group of organic compounds including vitamin C, E, carotenoids, folic acid (FA), B_6, B_{12}, D, and coenzyme Q_{10}, known for their antioxidant and cardioprotective roles [90].

2.5.1. Vitamin D

In a mouse model of autoimmune myocarditis, 1, 25-Dihydroxyvitamin D3 improved cardiac function, suppressed cardiac inflammation, regulated autophagy dysfunction by reducing the expression of Beclin-1, LC3-II and p62 proteins, attenuated myocardial apoptosis, abrogated Th1 cell progress, increased Th2 cell development, enhanced B cells apoptosis, and restricted cell differentiation as well as autoantibody production [91]. In addition, deficiency or insufficiency of vitamin D (VitD) plays a pivotal role in the pathogenesis of inflammation in myocarditis. It seems that VitD receptor (VDR) mediates helpful regulatory effects of VitD on cardiomyocyte function, inflammation, and gene transcription. VitD exerts anti-myocarditis effects by upregulating

VDR on $CD4^+$ T cells and IFN-γ, restricting IL-4 and Th2 cell differentiation on $VDR^{-/-}$ mice;conversely, VDR deficiency induced myocarditis associated with Th2-biased inflammation [92]. Therefore, upregulation of VitD has a therapeutic potential for the treatment of myocarditis due to its anti-inflammatory, anti-oxidant, anti-apoptotic, immunity and autophagy modulation properties.

2.5.2. Vitamin C

A meta-analysis on the clinical effects of vitamin C on children with viral myocarditis have indicated that levels of LDH, AST, CK, CK-MB, CD4, CD4/CD8, CD3, CTNI, and terms of the total effective rate were improved in children receiving intravenous vitamin C combined with conventional therapy. It also suppressed inflammatory cells and myocardial damage, enhanced immunity, increased coronary artery flow and relieved fatigue [93].

3. Clinical findings

There are few clinical studies on the role of natural phytochemicals in myocarditis. This review covered most of the studies focused on phytochemical ingredients relevant to myocarditis both in vitro and in vivo. A clinical report (non-RCT) on the effects of colchicine in treatment of recurrence myopericarditis on 60 male patients showed that a two-month administration of colchicine following discharge, improved LV function, incidence of heart failure, arrhythmia, cardiac tamponade and regulated the levels of maximum CRP and serum troponin I [94]. Moreover, administration of colchicine (0.5 mg twice daily for two years) as an adjunct to the conventional therapy in five heart failure patients (a case series of five patients, non-RCT), was associated with beneficial effects on overall survival and clinical status and also diminished the occurrence of rare and severe forms of complications in viral myocarditis [51]. By contrast, a randomized clinical trial has reported that one month consumption of colchicine (1 mg once daily) in twenty-three patients with myocardial infarction and inflammation revealed no clinical improvement during the study period [54]. Even so, larger studies are needed to clarify the impact of colchicine on myocarditis and cardiac inflammation. Furthermore, the findings of fourteen randomized controlled trials (Until 2012) on the role of herbal medicines on viral myocarditis with a minimum of seven days of treatment each, indicated that *Astragalus membranaceus* (either as an injection or granules) active polysaccharide and triterpenoid relieved cardiac symptoms, reduced myocardial enzymes, CPK levels, adverse effects and improved cardiac function [95]. Additionally, the clinical evidences on berberine revealed beneficial cardiovascular effects owing to its anti-oxidant and anti-inflammatory properties however, there are no clinical trials on the effects of berberine on myocarditis [50]. There is a deficiency of standard guidelines and clinical trials to assure the efficacy and quality of plant derived medicinal products for prospective anti-myocarditis applications. Phytochemicals have shown significant immunomodulatory, anti-inflammatory, and antioxidant effects in animal and human studies. They can be added to conventional treatments as 'complementary medicine' in myocarditis. Nevertheless, additional clinical studies are required to determine appropriate regimens in terms of dosage, frequency and duration in treatment of myocarditis with phytochemicals.

4. Toxicity

Given the lack of adequate clinical trials, only few studies addressed toxicity profile of phytochemicals. Nicotine is known for multifaceted cardiovascular adverse effects and is associated with CVDs in chronic users, however recent nicotine therapy is an emerging approach in treatment of myocarditis likely through cholinergic stimulation [54,55]. Also, it is reported that colchicine considerably aggravates pancreatic and cardiac CVB3 infection and viral load in mice models since it induces splenic apoptosis, increases neutrophils, and reduces infiltrated leukocytes and megakaryocytes in the red pulp of spleen both in uninfected and CVB3-infected mice. Therefore, these results support colchicine-induced toxicity on megakaryocytes and its inhibitory role on their entry into the spleen [103]. Conversely, some studies have indicated no histopathological damage with high doses of colchicine and may be safe in animal models [103]. Taken together, colchicine toxicity or safety in strains is still unclear and warrants extensive research.

5. Limitations

Although this Review highlighted selected natural products as promising therapeutic agents for myocarditis, there are some limitations, which should not be overlooked. For instance, there is a lack of sufficient well-designed and high-quality clinical studies that focused on the anti-myocarditis effects of natural products and nutraceuticals. Moreover, the safety and pharmacokinetics of some nutraceuticals still remain uncertain in clinical practice. Additionally, most of the animal experiments utilized IP administration route of nutraceuticals, and therefore the animal evidence is inconclusive and may not be directly translated to clinical trials. Another limitation is that the toxicity features of some nutraceuticals were not covered in both animal experiments and clinical trials.

6. Conclusions

Natural products and folk medicine are promising candidates to design and develop future therapeutic agents for treatment of CVDs particularly myocarditis [104–106]. To date, several plant derived compounds have demonstrated multiple regulatory mechanisms including immunomodulatory, anti-inflammatory, antioxidant and antiviral effects [107]. This review highlighted the significance of phytochemicals as anti-myocarditis compounds with diverse clinical application, few adverse side effects and high safety/efficacy both in animal and human studies. Nonetheless, in order to facilitate application of phytochemical, comprehensive trials addressing novel isolation techniques, precise delivery strategies and appropriate formulation are needed to improve their efficacy and bioavailability in practice.

Considering the lack of robust clinical data on the anti-myocarditis effects of nutraceuticals, further standard trials on nutrivigilance and quality control checklists should be available to assure the efficacy and quality of these products for prospective pharmaceutical use [108].

To conclude, natural phytochemicals may represent favorable therapeutic agents in combination with conventional therapy in myocarditis and its associated complications, what might be especially important now in the time of pandemic and the higher risk of myocarditis both in the acute Covid-19 and during Long-Covid [109,110].

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AS AE conceived and designed the study. AE and AS were involved in preparing the initial draft. MB and TJ revised the final version. All authors approved the final version.

Conflict of interest statement

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