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FULL PAPER

Beneficial effects of nano-phytosome of Quercetin on inflammatory parameters in mouse model of multiple sclerosis

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This study evaluated the beneficial effects of quercetin nano-phytosome on inflammatory parameters in multiple sclerosis. The animals were divided into five groups, including Control, 150 Quercetin, 300 Quercetin, 150 and 300 nano-phytosome of Quercetin. At the end of the study, serum levels of Granulocyte-macrophage colony stimulator (GMCSF), interleukin 1β (IL1β), interleukin 2 (IL2), interleukin 6 (IL6), interleukin 10 (IL10), interleukin 17 (IL17), Interleukin gamma (IFNγ) and tumor necrosis factor alpha (TNFα) were determined. The results showed that administration of Quercetin and its nano-phytsome significantly decreased the levels of IL-1β, IL-2, IL-6, IL-17, IFN-γ, TNF-α and GM-CSF and increased IL-10 in comparison to the control group. The treated animals with nano-phytsome significantly decreased IL-2, IL-1β, IL-17, IL-6, IFN-γ, TNF-α and GM-CSF and increased IL-10 compared with Quercetin group. Quercetin nanophytosomes can be used to effectively improve inflammation. We recommend using quercetin nanophytosomes to reduce inflammation in patients with multiple sclerosis.

KEYWORDS

Cytokines; Quercetin; nano-phytosome; Mice; TNF-α.

Introduction

One of autoimmune diseases is multiple sclerosis (MS) that influences central nervous system (CNS) [1]. It is observed through different signs such as neurologic disabilities [2]. Experimental autoimmune encephalomyelitis (EAE) is an animal model to investigate inflammation, demyelination, and paralysis in MS [3]. This inflammation originates from T-cell and B-cell infiltrates in CNS [4]. Inflammation is significantly higher in early phase compared with late stages [4]. $CD8^+$ T-cells and with lower proportion of $CD4^+$ T-cells and B-cells are involved in the inflammatory infiltrates [5]. Previous studies have shown the effects of anti-inflammatory agents target T- and B-cells or only B-cells

[6], but therapies especially seek $CD4^+$ T-cell mediated inflammation [7]. Patients with MS have higher levels for prostaglandins and leukotrienes in CNS that increase severity of the disease. Anti-inflammatory agents with targeting the arachidonic acid pathway have been suggested for treatment of MS [8]. Flavonoids can protect human health and also have a major role in protecting, fighting against allergy and preventing inflammation [9]. Quercetin (3,3',4',5,7-Pentahydroxy flavone), a polyphenol, is produced in some plant species [10]. A study showed similar mechanism to steroidal anti-inflammatory drugs (NSAID) for Quercetin that prevented cyclooxygenase enzymes I and II as mediators for production of inflammation [9]. Quercetin as a polyphenol has been shown in a few animal models to have several potential anti-inflammatory as well as anticarcinogenic applications [10]. Quercetin may alleviate inflammation, but its use has limitations, especially considering major limitations in bioavailability and absorption [11]. Quercetin is slowly absorbed due to poor lipid solubility, the increase in molecules hydrophilicity, non-absorption through passive diffusion from intestine into bloodstream, and degradation of phenol via gastrointestinal [12]. A novel formulation for Quercetin is needed that protects it from damages [13]. Preparation of particles in the nano-size improves bioavailability of agents in crossing permeability barriers [14]. Phytosome is known as a botanical formulation for the production of lipophilic molecular complex for increasing absorption and bioavailability of some plant compounds [15]. It seems that Quercetin is a safe agent for improvement of antioxidant properties that are involved in the inflammation process. The current study aimed to assess the effects of Quercetin nano-phytosome on inflammatory parameters in animal model of multiple sclerosis.

Materials and methods

Materials

Soybean phosphatidylcholine, cholesterol, methanol and dichloromethane were prepared from Merck Company. Quercetin was purchased from Sigma Aldrich Company (Germany). Other chemicals used and solvents were prepared from analytical grade.

Fabrication and characteristics of nano-phytosome of Quercetin

Phytosomes were based on previous studies by different molar ratios of Quercetin, phosphatidylcholine and cholesterol, as previously reported [16]. Summary, Quercetin and phosphatidylcholine were dissolved in methanol. The resulting mixture was taken in a round bottom flask and evaporated at 45°C. The lipid resulted from thin layer was submitted to nitrogen gas flow. Distilled water was used for hydration film in a rotary at 45°C. Sonication and homogenization were used for decreasing phytosomes size.

A particle size analyzer was used for the evaluation of particle size and its distribution. Volume median diameter (VMD) and SPAN value were used for evaluating the size distribution as follows:

$$\text{Eq. 1: SPAN}=\frac{D\,(V90\%)-D(V10\%)}{D\,(V50\%)}$$

In this equation, D (v 90%), D (v 10%) and D (v 50%) are equivalent volume diameters in volumes of 90, 10 and 50%, respectively.

The encapsulation efficiency (EE) was investigated as follows:

$$\text{Eq. 2: EE (\%)}=\frac{W\,(added\ drug)-W(free\ drug)}{W\,(added\ drug)}\times 100$$

In this equation, W (added drug) is the amount of drug added when preparing phytosomes, and W (free drug) is the amount of free drug assessed in the lower chamber of the Millipore Amicon® after centrifugation.

Animals

A total number of sixty six-week-old female C57/Bl6 mice were used in this study. All the animals were pathogen-free and had a weight of 25±2 g. Animals were maintained at 20±2°C and a 12h light and dark cycle.

EAE Model

The EAE model was induced as reported by Fonseca-Kelly et al., (2012). Animals were anesthetized by 0.2 ml solution containing 10 mg/ml ketamine and 1 mg/ml xylazine. Animals were immunized by using 300 µg myelin oligodendro glialglycoprotein (MOG) peptide in complete freund's adjuvant (CFA; Difco, Detroit, MI, USA) having 2.5 mg/ml *mycobacterium tuberculosis* (Difco), divided into two doses injected subcutaneously at two separate sites on the back. The mice were administrated with 200 ng pertussis toxin (List Biological, Campbell, CA, USA) in 0.1 ml PBS. Clinical scores were in a range from 0 to 7, 0 as lack of disease (normal); 1=impairment of tail motion; 2=paralyzed of tail; 3= disruption of movement; 4=paralyzed of one leg; 5=paralyzed of both leg; s 6=full paralyzed of hands and feet; 7=death.

Acute toxicity test

Lorke method was used for evaluating the acute toxicity test [17]. Summary, after 24 h fasting, 36 mice were divided into 6 groups and orally received 100, 200, 300 mg/kg nano-phytosome of Quercetin and Quercetin in phosphate buffered saline (PBS). Mice were monitored for toxicity and behavioral signs such as locomotor activity, changes in physical appearance respiratory distress, coma, and mortality for 72 h. We did not observe any toxicity and behavioral signs; therefore, we used doses 150 and 300 mg/kg Quercetin nano-phytosome and Quercetin for future experiments.

Groups and treatment

The animals were divided into five groups, 12 animals per group. Experimental groups included: 1) The control one where animals received PBS (Control), 2 & 3) Mice orally received 150 and 300 mg/kg Quercetin dissolved in PBS (150 and 300 Q) and 4 & 5) Mice orally received 150 and 300 mg/kg Quercetin nano-phytosome dissolved in PBS (150 and 300 NQ).

Investigation of cytokines in serum

Four weeks after immunization with different doses of MOG/CFA, the serum levels of Granulocyte-macrophage colony stimulator (GMCSF), interleukin 1β (IL1β), interleukin 2 (IL2), interleukin 6 (IL6), interleukin 10 (IL10), interleukin 17 (IL17), Interleukin gamma (IFNγ) and tumor necrosis factor alpha (TNFα) were determined by commercial kits (IBL International, Hamburg, Germany) on the basis of the producer guidelines.

Statistical analysis

We analyzed our data by one-way or two-way ANOVA and and Tukey post hoc by help of SPSS software. The findings are shown as mean ± SD and significant considered as $P<0.05$.

Results

Charactristics of nano-phytosome of Quercetin

The data for characteristics of nano-phytosome of Quercetin showed that the mean of particle size, SPAN and encapsulation efficiency were 89.31±2.35 nm, 0.83±0.02 and 96.67±0.58%, respectively.

Scores

We induced EAE in all the mice immunized with MOG/CFA. The results showed significant differences between control and treatment groups (Figure 1). Treatment with nano-phytosome of Quercetin and Quercetin could significantly decrease clinical scores compared with control group (P<0.05). The results showed that clinical scores were observed from day 9 in control group (P<0.05), while it was observed at day 13 in 150 Q group and day 19 in 300 NQ (P<0.05). The lowest clinical scores were observed in NQ groups.

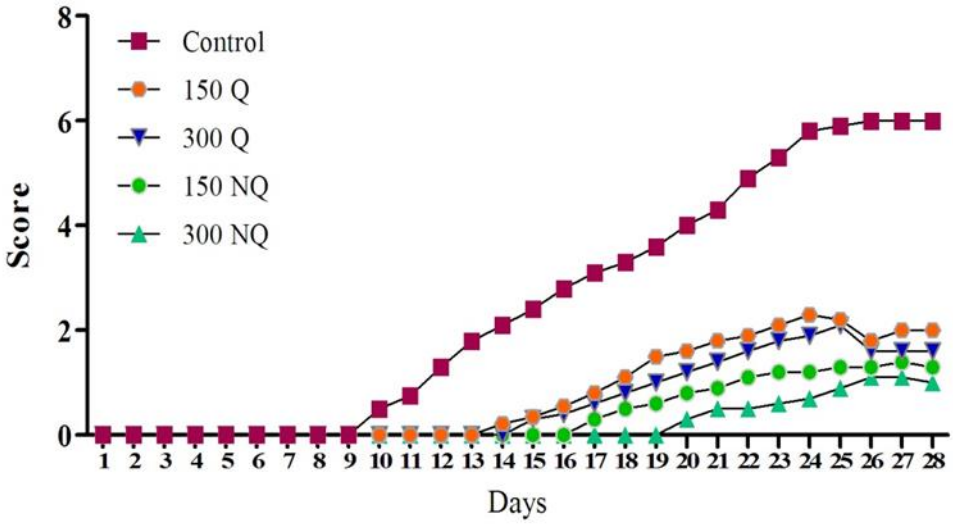

FIGURE 1 Experimental score in EAE model. The results indicated that Quercetin and nano-phytsome of Quercetin decreased scores. All data were expressed as mean ± SD

Inflammatory responses

Figure 2 depicts the results for inflammatory responses (A-H). The administration of Quercetin and Quercetin nano-phytsome significantly could reduce the serum levels of IL-2, IL-6, IL-17, IL-1β, IFN-γ, TNF-α and GM-CSF and raised the levels of IL-10 versus the animals in the control group (P<0.05). In addition, the animals treated with Quercetin nano-phytsome showed lower GM-CSF, IL-1β, IL-2, IL-6, IL-17, IFN-γ and TNF-α and greater the levels of IL-10 rather than Quercetin group (P<0.05). The treatment with greater levels of Quercetin nano-phytsome (300 mg/kg) could decrease IL-2, IL-6, IL-17, IL-1β, IFN-γ, TNF-α and GM-CSF and raised the levels of IL-10 rather than other levels of Quercetin (150 mg/kg) (P<0.05). We did not observe significant differences between animals treated with 300 mg/kg and levels 150 mg/kg (P>0.05).

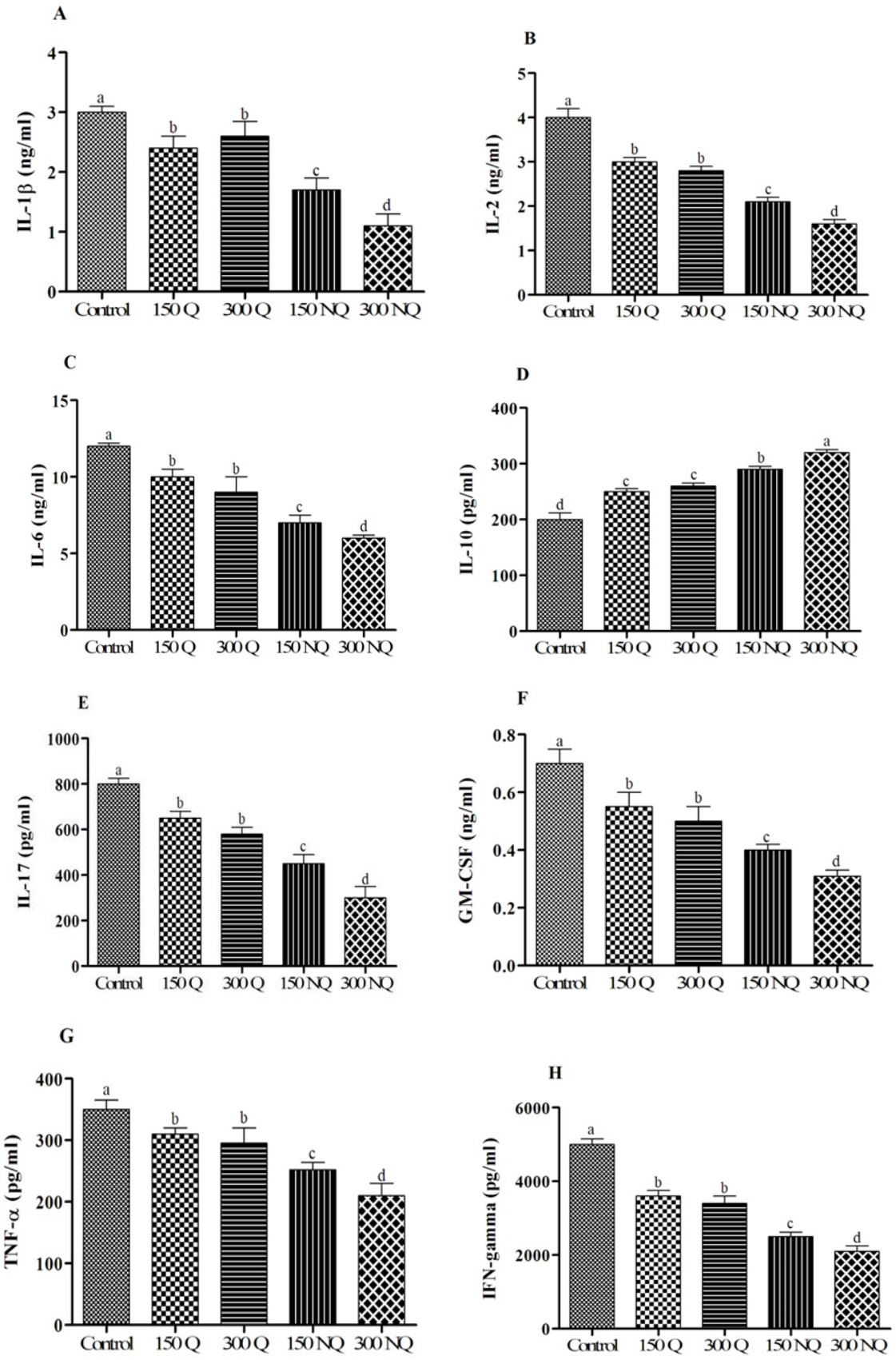

FIGURE 2 The effects of Quercetin and nano-phytsome of Quercetin on inflammatory cytokines in EAE model. A) IL-1β; B) IL-2; C) IL-6; D) IL-10; E) IL-17; F) GM-CSF; G) TNF-α and H) IFN-γ. The different superscripts (a-e) show significant differences among groups at level of 0.05

Discussion

The impacts of quercetin nano-phytosome on inflammatory parameters in mouse model of MS were evaluated. Our findings showed that using of Quercetin nano-phytosome decreased inflammation in MS model. We prepared nano-phytosome of Quercetin in a mean of particle size of 89.31±2.35 nm, SPAN of 0.83±0.02 and encapsulation efficiency of 96.67±0.58%. The particle size for nano-phytosomes is important and can influence stability and bioavailability of agents loaded into it [16]. It was reported that smaller particles have a large surface area and also better release and higher stability [18]. The particle size was 89.31±2.35 nm that is appropriate for nano-capsulation. These results show that quercetin has appropriate affinity for phytosomes that could be attributed to its planar configuration and could be simply placed into compounds organized of the phospholipids into phytosomes membranes [19]. The encapsulation efficiency was 96.67±0.58% that shows an appropriate efficiency. The average for disease severity in the control group was significantly higher compared with mice treated. Injuries severity was significantly higher in the control group. Control animals not only had higher severity, but also showed signs in earlier days. These findings show that Quercetin and its nano-phytosome not only decrease severity, but also delays signs. The results for clinical scores did not show significant difference for the levels of Quercetin ($P>0.05$), but higher dose of nano-phytosome-Quercetin decreased signs compared with the lower dose. It means that the nano-phtosome helps to deliver higher levels of Quercetin. A significant relation can be seen between levels of nano-phytosome-Quercetin with clinical scores and inflammatory responses.

The results showed the serum concentration of IL-1β was 3.00±0.10, 2.40±0.20, 2.60±0.40, 1.70±0.20 and 1.10±0.20 for control, 150 and 300 Quercetin, 150 and 300 Quercetin nano-phytosome, respectively. The IL-1 family of cytokines has pleiotropic effects on hematopoietic and non-hematopoietic cells associated with neuroinflammation. IL-1β is formed through both inflammasome-dependent and -independent routes upon activation of a variety of leukocytes [20]. IL-1β influences T_H cells for promoting pathogenicity in EAE model [21]. The results showed the serum concentration of IL-2 was 4.00±0.20, 3.00±0.10, 2.80±0.10, 2.10±0.10 and 1.60±0.10 for control, 150 and 300 Quercetin, 150 and 300 Quercetin nano-phytosome, respectively. IL-2 or T cell growth factor is mainly synthesized through activating CD4+ T cells and also induces T cell expansion [22]. IL-2 and its receptor play important roles in proliferation of autoreactive T cells and losing immune tolerance in patients with MS [22]. Studies have shown that a monoclonal antibody that targets IL-2Rα and prevented action of subunits is used for the treatment of MS [23]. The results showed that animals treated showed lower concentration for IL-6 compared with the control group and values were as follows; control (12.00±0.20), 150-Q (10.00±0.50), 300 Q (9.00±1.00), 150 NQ (7.00±0.50) and 300 NQ (6.00±0.20). IL-6 is known to be inducer in acute phase response that is formed via T and B cells, macrophages, microglia [24]. The role of IL-6 was elucidated following discovery IL-6-deficient animals showed resistance to EAE [25]. The results showed the serum concentration of IL-10 was 200.00±12.00, 50.00±5.00, 260.00±6.00, 290.60±6.00 and 320.00±7.00 for control, 150 and 300 Quercetin, 150 and 300 Quercetin nano-phytosome, respectively. It is an anti-inflammatory cytokine that reduces the levels of TNF, IL-1β, IL-6, IL-8, IL-12, and IL-23 [26] as seen for TNF, IL-1β, IL-6 in the current study. It was reported that IL-10 production decreases prior to relapse and increases during remission in MS patients [22]. The results showed that animals treated

showed lower concentration for IL-17 compared with control group and values were as follows: Control (800.00±25.20), 150-Q (650.00±30.50), 300 Q (580.00±30.00), 150 NQ (450.00±40.00) and 300 NQ (300.00±50.20). IL-17A produces cytokines including IL-6, IL-21 and IL-22, GM-CSF, and TNF-α [27]. Secretion of circulating IL-17 and IL-22 increased in MS patients and it correlated with active brain injuries [22]. On the other hand, neutralization of IL-17 via antibodies or faulting IL-17 could decrease EAE signs [28]. It was reported that an anti-IL-17 decreases lesion activity in MS patients [29]. The results showed the serum concentration of GM-CSF was 0.70±0.05, 0.55±0.05, 0.50±0.05, 0.40±0.02 and 0.310±0.02 for control, 150 and 300 Quercetin, 150 and 300 Quercetin nano-phytosome, respectively. GM-CSF has a key role in keeping inflammation through controlling a group of cytokines and chemokines involved in the activation, recruitment, and local proliferation of macrophages [30]. The results showed that animals treated showed lower concentration for TNF-α compared with the control group and values were as follows: Control (350.00±15.00), 150-Q (310.00±10.00), 300 Q (295.00±25.00), 150 NQ (252.00±12.00) and 300 NQ (210.00±20.20). TNF-α is a proinflammatory cytokine that is mainly made by immune cells such as macrophages, T and B cells, astrocytes, and neurons [27, 31]. Studies have reported a positive correlation between levels of TNF-α and lesions in MS patients that had positive correlation with severity and progression of the disease [27], as seen in the current study. The values for serum concentration of IFN-γ was 500.00±150.00, 3600.00±150.00, 3400.00±200.00, 2504.00±120.00 and 2100.00±150.00 for control, 150 and 300 Quercetin, 150 and 300 Quercetin nano-phytosome, respectively. In sum, all the results show that EAE model increases inflammation and the use of Quercetin and specially its nano-phytosome in higher levels alleviate inflammation. Parallel to our findings, Davoodi et al., [10] showed that nano-phytosome of Quercetin could decrease inflammation in Mouse Model of malaria. Our findings showed that Quercetin especially in nano-phytosome form could decrease inflammation. The underlying mechanism is unknown but these results show that Quercetin has anti-inflammatory effects and the use of nano-phytosome can be a profit strategy for delivering it.

Conclusion

In summary, nano-phytosome of Quercetin was fabricated in a mean of particle size of 89.31±2.35 nm, and encapsulation efficiency of 96.67±0.58%. There was positive correlation between clinical scores and inflammation severity. Our findings showed that using nano-phytosome of Quercetin reduced inflammatory parameters. It can be suggested using Quercetin nano-phytosome as an anti-inflammation agent in patients with MS can be effective.

Author contributions

All the authors had similar share in design, conducting, analyzing, writing and revising.

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