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Nutritional bioactive compounds with beneficial effects for multiple sclerosis: Potential implication of G-Quadruplexes?

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease resulting in myelin destruction and consequent physical disability. Several nutritional molecules modulate genes of reported relevance in MS eliciting beneficial effects. Intriguingly, some of these molecules are able to bind G-Quadruplexes (G4), specific DNA secondary structures involved in the regulation of gene expression and function. For instance, epigallocatechingallate and thymoquinone are known to interact with G4 *in vitro*, while sanguinarine, quercetin, curcumin and coumarin-quinolinium derivatives interact with G4 *in vivo* affecting oncogene expression. Noteworthy, several genes involved in MS present G-rich sequences known to fold into G4. Thus, we suggest and speculate that G4 targeting through daily intake of nutritional bioactive molecules might represent a novel therapeutic approach to improve MS symptoms and progression.

1. Introduction

Multiple sclerosis (MS) is the most common immune-mediated neurodegenerative disease of young adults worldwide. The inflammatory demyelination damage in the central nervous system (CNS) is responsible for motor impairments, muscle weakness and cognitive decline resulting in significant physical disability and, in turn, poor quality of life [1]. MS pathogenesis is characterized by increased migration of autoreactive lymphocytes across the blood–brain barrier (BBB) [2]. Activated lymphocytes and myeloid cells produce autoantibodies directed against different components of CNS and the resulting inflammatory environment causes degeneration of myelin, axons, synapses, oligodendrocytes and neurons [3].

MS aetiology is multifactorial, involving genetic, epigenetic, and environmental factors. Genome-wide association studies allowed the identification of more than 200 genetic risk variants associated with MS susceptibility, mainly including immunological relevant genes [4]. The strongest association has emerged with polymorphisms in human leucocyte antigens (HLA) genes, in particular HLA-DRB1*15:01 [5]. Ongoing studies aim to clarify how genetic affects individual phenotypes and prognosis.

In parallel, the increased incidence of MS observed over the past few decades and the variability of prognoses, not imputable to genetic substrate or to differential therapies, highlighted the importance of environmental risk factors. Among these factors, viral infections, helminths infection, sunlight–UV exposure, cigarette smoking, obesity in early adolescence, vitamin D insufficiency and diet-related changes account for the development and the severity of the disease [6]. Thus, the going assumption is that MS results from the action of environmental factors in genetically susceptible individuals. The significant variability in the clinical course of MS prompted to the identification of potentially modifiable environmental factors to mitigate outcomes upon diagnosis. In this context, diet emerged as a relevant key factor for both MS onset and progression. Several bioactive dietary components included in our daily nutritional source are beneficial for MS, being able to attenuate inflammation and neurodegeneration thus promoting CNS re-myelination (Table 1). Recently, the rise of nutrigenetics and nutrigenomics further highlighted the relevance of diet in maintaining health and in preventing and/or treating disease and prompted studies on the molecular mechanisms targeted by single dietary components. Bioactive dietary components can modulate gene expression activating specific transcription factors by signalling cascades or by direct binding. Alternatively, they can regulate epigenetic factors, such as non-coding RNA, DNA methylation, histone modification and, in turn, modify the chromatin structure [7]. Interestingly, nutritional factors may also affect the formation and stabilization of secondary structures formed by DNA or

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Table 1
MS-relevant genes, pathological role, and G4 detection.

Gene	Function in MS	G4 localization	G4 detection method
NRF2	NRF2 deficiency exacerbates MS	Promoter, 5′UTR	CD, UV melting experiments, nuclear magnetic resonance
VEGF	Controversial role in MS	Promoter	Nuclear magnetic resonance, electrospray ionization, mass spectrometry
IL-17	IL-17 reduction amilioretes EAE	Promoter	Bioinformatics analysis
TGF-β1	Potential protective role in MS	Promoter	Bioinformatics analysis
TGF-β2	Potential harmful role in MS	5′UTR	CD, UV spectroscopy

RNA known as G-quadruplexes (G4) and their balance in the human genome, thus regulating gene expression [8]. G4 represent epigenetic markers, since their formation can influence nucleosome assembly and DNA methylation, cause site mutagenesis, rearrangement and copy number alterations, which lead to genome instability and diseases pathogenesis [9,10].

In this review, we highlight that some bioactive dietary components beneficial for MS are able to specifically bind G4 motifs. Furthermore, we evidence G4 abundance in genes related to MS. Thus, we speculate about G4 as a potential therapeutic target of bioactive dietary components in MS.

2. Physiopathological role of G4

G4 are four-stranded, inter- and intramolecular structures formed in G-rich DNA and RNA sequences. In these sequences, four tracts of two or more guanine bases separated by one or more nucleotides fold to form a G-tetrad, a planar structure held together by Hoogsteen hydrogen bonds. Stacked G-tetrads connected by loops form a G4 structure. The number of G-tetrads, the length and sequence composition of the loop affect the stability of the folded G4 motif, usually higher numbers of G-tetrads and shorter loop lengths tend toward major stability. G4 motifs can assume different topologies: parallel, antiparallel or hybrid depending on the directionality of the G-strands; topology and stability are influenced by cations like Na^+ or K^+ embedded in the G-tetrads [11]. The distribution of G4-forming sequences is not random in the genome but observed within functional regions, like up-stream gene promoter regions, intron and exon borders, and the 5'and 3'UTRs of transcriptionally active genes [12], predominantly cancer related genes [13]. G4 role is ascertained in biological processes like transcription, replication, recombination, and maintenance of chromosome stability. However, the presence of G4 structures in genome and transcriptome of all cell types suggests their involvement in numerous cell functions and in the progression of pathological conditions.

In the last few years, studies addressing the therapeutic potential of G4 motifs and/or their specific targeting for the treatments of several diseases have extensively increased. Indeed, G4 motifs are associated to several diseases like cancer, viral diseases, and neurological disorders. G-rich sequences are abundant in the promoters of oncogenes, thus several studies focused on the design of selective small molecules able to stabilize G4 motifs to obtain anti-cancer effects. In brief, G4 motif stabilization blocks telomerase activity [14] and its access to the G-rich single strand, thus preventing telomere extension and cancer cell immortality [15–17].

The existence of G4 structures in various viruses like Ebola, Zika, Herpesvirus, human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus (SARS-CoV) attracted attention and suggests the use of G4 interacting ligands for anti-viral therapies and controlling the aetiology of several diseases [17].

Interestingly, G-rich sequences that may fold into G4 motifs are detected also in genes involved in neurodegenerative diseases. Two mechanisms were proposed to explain G4 involvement in neurological diseases: i) amplification of G-rich sequences predicted to form G4 motifs and found to be causal of disease, and ii) mutations that affect the expression levels of G4 binding proteins. These mechanisms were reported for repeat expansions of a GGGGCC sequence in the first intronic region of the gene C9orf72 that causes amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and for extended repeat of CGG in the 5′-UTR exonic region of the gene fragile X mental retardation 1 (FMR1) in Fragile X syndrome (FXS), with loss of expression of FMRP, a G4 binding brain protein [18,19]. The implication of G4 was also proposed in Parkinson disease (PD), where RNA G4 assembly was reported to form scaffolds for the aggregation of α-synuclein encoded by the α-synuclein (SNCA) gene, thus contributing to neuronal dysfunction and neurodegeneration [20]. The involvement of G4 in Alzheimer disease (AD) was suggested by the detection of a parallel G4 in the 5′-UTR region of the metalloprotease domain containing protein 10 (ADAM10), that negatively regulates ADAM10 inhibiting the cleavage of the anti-amyloidogenic amyloid precursor protein (APP). Additionally, a G4 motif in the 3′-UTR of *APP* mRNA directly inhibits APP translation. Moreover, beta-secretase 1 (BACE1) exhibits a G4-forming potential harbouring G-rich sequence on its third exon that might activate full-length (501) transcript production during alternative splicing driving enhanced APP proteolysis and amyloid beta (Aβ) production [21]. A schematic representation of G4 implication in above-mentioned neurodegenerative diseases is provided showing genes involved and the effects of their dysregulation (Fig. 1).

3. G4 motifs in MS relevant genes

Interestingly, genes involved in MS pathogenic mechanisms display sequences prone to form G4 structures, however, the potential impact of G4 motifs on the regulation and function of these genes in MS in completely unexplored. For instance, nuclear factor erythroid 2-related factor 2 (NRF2), vascular endothelial growth factor (VEGF), interleukin-17 (IL-17), and transforming growth factor-beta (TGFβ) exert multiple roles in MS as described in Table 1.

NRF2 is a transcription factor that in response to oxidative stress translocates to the nucleus activating antioxidant enzymes thus neutralizing reactive oxygen species (ROS) [22]. In NRF2-deficient experimental autoimmune encephalomyelitis (EAE) mouse model, a more rapid onset and exacerbated clinical severity were observed along with enhanced number of lesions, infiltrating immune cells, higher microglial activation, and visual dysfunction. Notably, in the EAE lesions, the damaged oligodendrocytes showed relatively low levels of NRF2 that might implicate high vulnerability of these cells to oxidative stress [23,24]. These studies suggest that approaches aimed to modulate endogenous NRF2 activation might protect the brain against oxidative damage.

VEGF is a potent endothelial cell growth factor known to increase angiogenesis, stimulate blood vessel growth, regulate vascular permeability and facilitate inflammation in various diseases [25,26]. Several studies suggest a role of VEGF in MS pathogenesis and in the regulation of inflammation. However, contrasting data were reported [27,28].

The inactivation of astrocytic VEGFA expression reduced BBB breakdown, lymphocyte infiltration and ameliorated paralysis in a mouse model of MS, thus suggesting inhibition of VEGFA signaling as a protective strategy in MS [28–30]. However, other studies showed decreased expression of VEGFA in cerebrospinal fluid (CSF), peripheral blood mononuclear cells (PBMC) [31,32] and serum [33] from MS patients.

IL-17 and TGFβ are both involved in inflammatory diseases. IL-17 is mainly produced by T helper 17 (Th17) cells and plays a key role in host defence against microbial infections. IL-17 is involved in EAE development and its therapeutic neutralization reduced severity in EAE [34]. In MS patients, higher IL-17 levels were detected in both CSF and serum

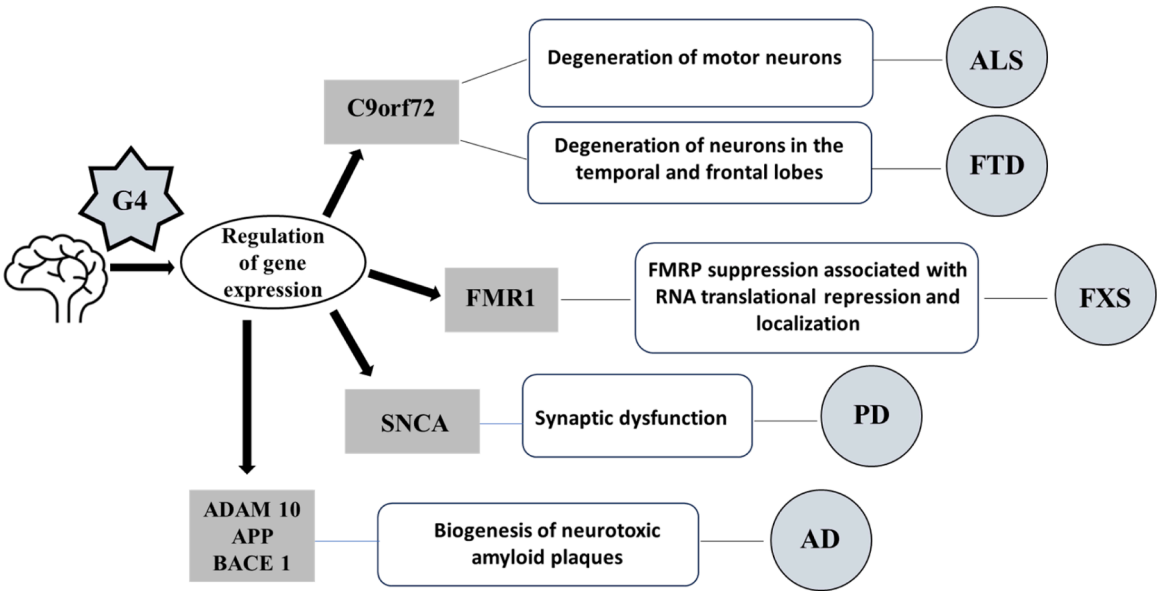

Fig. 1. G4 involvement in neurodegenerative diseases. G4 motifs can regulate genes involved in ALS, FTD, FXS, PD and AD compromising their function and contributing to the deleterious effects of these neurodegenerative diseases.

during relapses compared to control subjects with other non-neurological diseases [35]. TGF-β plays a role in inflammatory responses through the activation of microglia in MS animal models [36]. In EAE, systemic administration of TGF-β1 prevented disease severity [37] and promoted re-myelination, restoring neurological function [38]. In particular, TGF-β1 and TGF-β2 were differently expressed in leukocytes and plasma of relapsing-remitting MS (RRMS) patients; both were down-regulated in leukocytes while up-regulated in blood plasma [39]. Studies on patients with a progressive form of MS showed that TGF-β2, but not TGF-β1, was increased in brain periplaques. Further studies suggest that inhibition of TGF-β1 might bear the risk of triggering neuro-inflammation, while the inhibition of TGF-β2 might breakdown astrocytosis and prevent periplaque-associated myelin damage [40].

Overall, the above-mentioned genes show potential G4 forming sequences in their promoters as highlighted by several studies. In the promoter region of NRF2 the formation of a parallel intramolecular G4 motif in the presence of K^+ ions was highlighted by circular dichroism (CD) spectroscopy, ultraviolet (UV) melting experiments and nuclear magnetic resonance (NMR) [41]. The 5′UTR of NRF2 mRNA can display G4 motifs that, interacting with EF1a, promote Nrf2 protein translation under oxidative stress [42]. However, an in-depth exploration of G4 structure distribution and function in the regulation of NRF2 expression is still lacking, and further studies are needed.

DNA G4 motifs were detected in the proximal promoter region of VEGF and adopted a parallel-stranded structure in K^+ solution as obtained by NMR [43] and electrospray ionization mass spectrometry [44]. Once clarified the role of VEGF in MS, the targeting of G4 motifs might allow the modulation of VEGF expression to obtain beneficial effects in MS.

A computational study described putative G-quadruplex-forming sequence (PQFS) in the promoters of cytokines and chemokines like IL-17 and TGF-β1 that were comparable to those observed in proto-oncogenes [45]. Bioinformatics analysis revealed G4 in the 5′ UTR of TGFβ2 mRNA. UV and CD spectroscopy demonstrated the ability of this stretch of sequence to form intramolecular parallel highly stable G4, surprisingly able to enhance TGFβ2 gene expression [46,47]. We might speculate that the presence of PQFS in the promoters of IL-17 and TGF-β1 suggest the possibility to interfere with the potential G4 motifs to reduce the levels of these cytokine to obtain beneficial effects in MS. On the other hand, potential destabilization of G4 at TGFβ2 might enclose MS amelioration.

4. Bioactive dietary compounds targeting G4

Naturally occurring compounds as those reported in Table 2 are part of human diet and are beneficial for MS due to their ability to interact and regulate genes and transcription factors relevant for MS. Examples of this modulation are represented by resveratrol [48] and curcumin [49] that increase the levels of NRF2. Natural polyphenols derived from red wine and green tea showed antiangiogenic activities inhibiting VEGF [50]. Thymoquinone was showed to improve EAE symptoms along with increased IL-17 and decreased TGF-β [51]. Similarly, nanocurcumin oral administration in MS patients increased IL-17 secretion levels [52].

Interestingly, some of these bioactive dietary compounds were demonstrated to specifically target G4 in vitro and in vivo. For some of these compounds the ability to bind G4 was characterized only by in vitro studies. For instance, the higher selectivity of epigallocatechingallate (EGCG) for G4 versus double stranded DNA was evidenced by mass spectrometry, CD spectroscopy and fluorescent assays [53]. Similarly, the interaction between thymoquinone and G4 was evidenced by spectral changes, melting temperature curves and docking simulations. Importantly, thymoquinone stabilized preferentially G4 over duplex intercalating near the TTA loop [54]. The ability of these natural compounds to bind G4 is particularly interesting since G4 targeting by synthetic small molecules has been deeply investigated, mainly in oncological fields with promising therapeutic results. These small molecules induce cancer cell growth arrest or modulate DNA damage responses. Importantly, some of these G4 interacting ligands such as quarfloxin were also employed in clinical trials for numerous types of cancers [17].

In particular, quarfloxin redistributes nucleolin within the nucleus, disrupting G4–nucleolin complexes, thus inhibiting c-MYC mRNA expression inducing apoptosis of cancer cells [55].

Recently, the interactions between bioactive dietary compounds and G4 motifs have been also better characterized. For instance, it has been clarified that sanguinarine binds to G4 via intercalation or end stacking mode by CD. Interestingly, sanguinarine induced G4 formation and stabilization and this interaction induced differentiation and quiescence in cancer cells [56–58]. Further studies showed that sanguinarine was able to bind G4 motifs at c-MYC, KRAS and telomeres. Similarly, biophysical studies and NMR spectroscopy reported that quercetin stabilized G4 motifs at c-MYC and telomeres and did not open the G-tetrad

Table 2
Natural compounds with beneficial effets in MS.

Natural compound	Source	Effects on MS	References
Resveratrol	Polyphenolic compound from blueberries, red grapes, rhubarb, mulberries, peanuts, and pistachios	Prevention of neuronal damage in EAE mice (via sirtuin 1) Reduction of oxidative stress Maintenance of blood brain barrier integrity ↓ Incidence, severity, and progression of EAE Increase of oligodendrocyte differentiation Pro-myelination effects	[34,65,66, 72]
Curcumin	Polyphenol from Curcuma longa	↓ Disease progression in MS patients ↓ Pro-inflammatory cytokines ↑ Sirtuin-1, Sox2 and forkhead box P3 expression ↑ IL-17 secretion levels ↑ Treg frequency and function ↑ TGF-β and IL-10 levels Antioxidant effects Improvement of patients' quality life	[35,73]
Thymoquinone	Phytochemical from Nigella sativa	Amelioration of EAE symptoms ↑ Anti-Inflammatory cytokines ↓ Pro-inflammatory cytokines	[51,74]
Sanguinarine	Benzophenanthridine alkaloid from the root of Sanguinaria canadensis	↓ Disease incidence ↓ Accumulation of microglia in the spinal cord ↓ Inflammatory cytokines Amelioration of clinical signs in EAE mice Pro-myelination effects	[75]
Quercetin	Flavonoid from capers, red onions, green tea, apples, berries, and red wine	Antioxidant and anti-inflammatory effects Pro-myelination effects	[76,77]
Coumarin	Organic compound from many plants, such as tonka beans, sweet clover, and cinnamon	↓ Clinical severity in EAE mice ↓ Inflammation ↑ IL-4 and IL-10 ↓ IL-1β and TNF-α Neuroprotective effects	[36–38]
Genistein	Isoflavone from soybeans, lupin, fava beans, kudzu, and coffee	Modulation of pro- and anti-inflammatory cytokines Amelioration of clinical signs in EAE mice ↓ Rolling and adhering of leukocytes	[78,79]
Epigallocatechin gallate (EGCG)	Polyphenol from green tea	Modulation of CD4+ T cell proliferation, differentiation, and cytokine secretion (alteration of IL-2 signaling) Amelioration of clinical signs in EAE mice	[39,80]

[59,60]. This interaction occurred in a stacking mode with monomeric G4, with the molecular plane being parallel with G-tetrads and in a groove binding with dimeric G4, with the molecular plane of quercetin being vertical with the planes of G-tetrads [48].

Other oncological studies reported curcumin ability to function as G4 stabilizer agent. Curcumin stabilizing effect occurs in the promoter of fibroblast growth factor receptor 3, thereby inhibiting its expression [49]. Similarly, curcumin stabilizes G4 motifs at KRAS [61] and several curcumin analogs are able to negatively modulate c-MYC expression through interaction with G4 motifs [50].

The stabilization of G4 motifs at KRAS and c-MYC was elicited also by other compounds. A very recent study reported the synthesis of a series of coumarin-quinolinium derivatives. One of these compounds showed exceptional ability in stabilizing G4 motifs at KRAS, suppressing its translation [62].

Recently, biophysical, computational and biological studies showed that resveratrol displayed high binding affinity for G4 motifs at c-MYC [63]. Notably, it has high ability to discriminate G4 versus duplex DNA [64].

Studies above described reported the ability of bioactive dietary compounds beneficial for MS to target G4 in the promoter of c-MYC and KRAS affecting the expression of these oncogenes. Interestingly, the potential relevance of c-MYC and KRAS in MS was recently suggested by few studies. More in detail, a study based on bioinformatics analysis suggested that KRAS might act as therapeutic target in MS [65] and c-MYC was demonstrated to be strongly up-regulated by CD28 signalling in RRMS patients [66]. Thus, the ability of the above-mentioned compounds to modulate G4 motifs at c-MYC and KRAS and potentially at other genes relevant in MS and harbouring G4 might contribute to their beneficial effect.

5. Conclusions

Diet is an environmental factor with relevant impact on MS onset and progression. Well-known diet bioactive components can regulate genes involved in MS, leading to an improvement of disease symptoms and progression. The molecular mechanisms underlying their action include modulation of transcriptional factors, epigenetic changes and modification of chromatin structure. G4 motifs are secondary structures able to initiate neuroprotective and/or neurotoxic cascades relevant for several neurodegenerative diseases.

Interestingly, some nutrients exhibiting beneficial anti-inflammatory, antioxidant, neuro-protective properties in MS patients can bind specifically G4 motifs. On the other hand, several genes involved in MS pathogenesis harbour G4 structures. These findings suggest that the intake of specific nutrients could regulate the expression and transcription of G4-rich genes relevant in MS, by G4 motif targeting (Fig. 2).

Importantly, G4 targeting with natural compounds offers non negligible advantages, indeed they are commonly used in traditional medicine for the treatment of many chronic diseases and are included into diet since ancient times, thus being tested for toxicity over time [67]. For some of these compounds, such as quercetin, the recommended optimal dose as a dietary supplement has been already established [68], while for others natural compounds further efforts are still necessary to standardize the dose and course of treatment. Although the hypothesis that nutritional factors may influence G4 structure formation and stability is plausible, the effects of specific nutrients on G4 motifs in

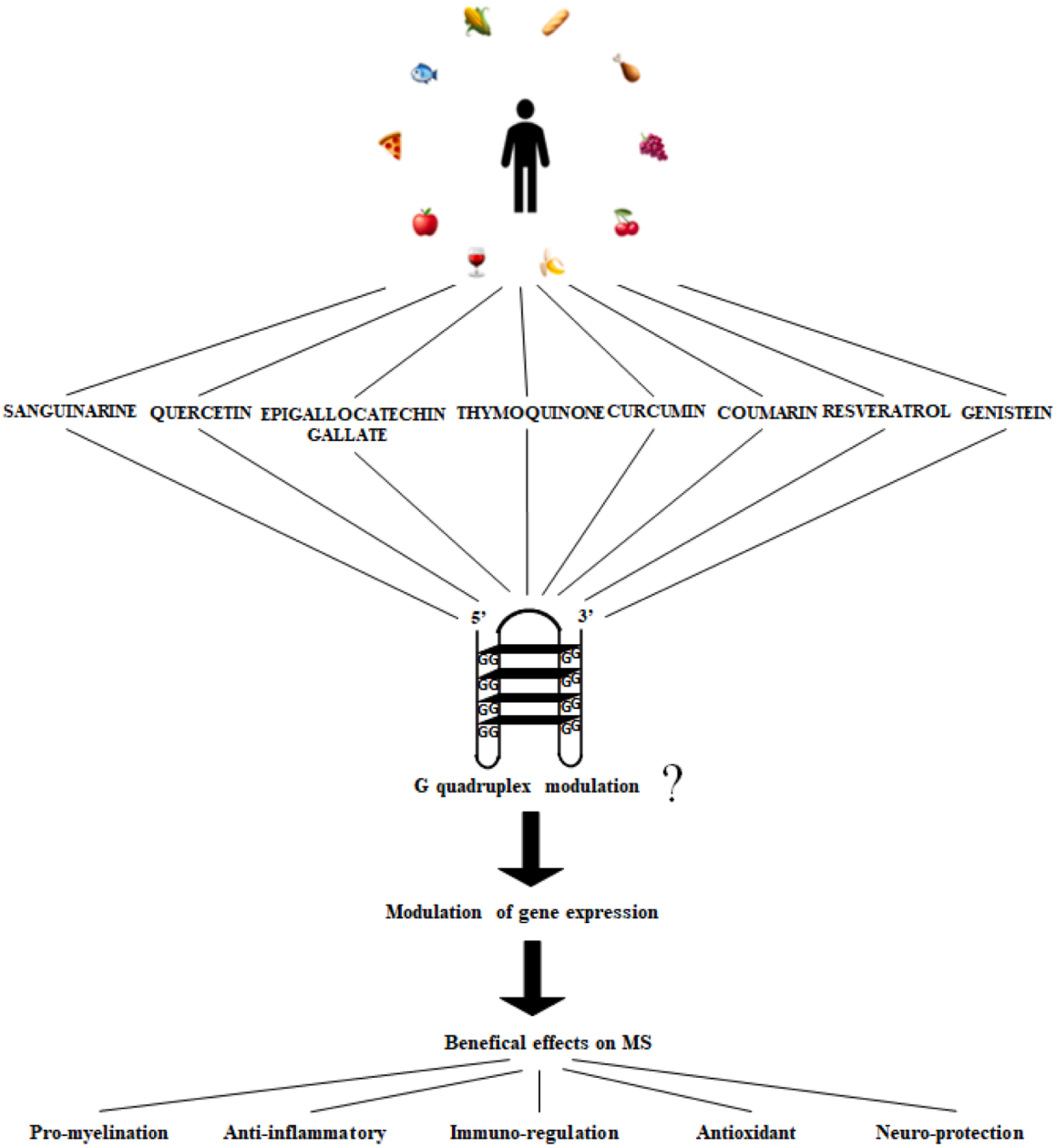

Fig. 2. Potential involvement of G4 motifs in the effect of bioactive compounds on MS. Natural bioactive compounds occurring in daily diets can interact with G4 motifs regulating gene expression and exhibiting potential beneficial effects in MS.

genes involved in MS needs to be addressed. Indeed, natural molecules represent a valuable starting point for the development of new and potentially more effective G4 ligands, offering promising avenues for drug development in MS. Numerous studies suggest that dietary factors modify epigenetic mechanisms such as DNA methylation and oxidation. Interestingly, these mechanisms often occur in proximity of G4 elements, affecting their stability and in turn, gene expression. Future investigation of the molecular mechanisms underlying nutrition impact on G4 will allow understanding if nutrients modulate G4 motifs acting on DNA epigenetic changes or through direct binding. However, the selectivity of these natural compounds toward G4 needs to be improved. To this aim, several studies focused on both shape and structures of the complexes formed by the ligands with G4, to understand which shapes and chemical bonding can improve the specificity of the interactions [69]. In parallel, the identification of G4 with special structural topologies or sequence compositions, such as vacancy G4 [70], bulge-containing G4 and stem-loop-containing G4 [71], featuring hallmarks different from the canonical G4, is moving forward, too. These studies might pave the way to personalized nutrition as an emerging tool for MS treatment, pointing out how diet could be an adjunct therapy, representing an intriguing chance to ameliorate the quality of life for MS patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

No data was used for the research described in the article.

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