










Review Article

Hormetic Effects of Bioactive Compounds from Foods, Beverages, and Food Dressing: The Potential Role in Spinal Cord Injury

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Spinal cord injury (SCI) is a damage or trauma to the spinal cord resulting in a total or partial loss of motor and sensory function. SCI is characterized by a disequilibrium between the production of reactive oxygen species and the levels of antioxidant defences, causing oxidative stress and neuroinflammation. This review is aimed at highlighting the hormetic effects of some compounds from foods, beverages, and food dressing that are able to reduce oxidative stress in patients with SCI. Although curcumin, ginseng, and green tea have been proposed for SCI management, low levels of antioxidant vitamins have been reported in individuals with SCI. Mediterranean diet includes food rich in vitamins and antioxidants. Moreover, food dressing, including spices, herbs, and extra virgin olive oil (EVOO), contains multiple components with hormetic effects. The latter involves the activation of the nuclear factor erythroid-derived 2, consequently increasing the antioxidant enzymes and decreasing inflammation. Furthermore, EVOO improves the bioavailability of carotenoids and could be a delivery system for bioactive compounds. In conclusion, Mediterranean dressing in addition to plant foods can have an important effect on redox balance in individuals with SCI.

1. Introduction

A spinal cord injury (SCI) is a condition that significantly impairs an individual's functional status, quality of life, and social independence (disability). The SCI can be divided into two main categories: the more common traumatic SCI typically caused by external physical impact [1] and nontraumatic SCI [2]. The different sites and the size of SCI can cause variable degrees of impairment from partial loss of motor or sensory function to complete paralysis below the injured spinal cord level, loss of bowel and/or bladder con-

trol, autonomic dysfunction (including in high SCI autonomic dysreflexia), and exaggerated reflex activities, as well as pain [3–8]. Based on these impairments, the interaction with the environment determines the different degrees of disability consequent to SCI. Regardless of the cause, the pathophysiology of SCI is characterized by two stages: an initial primary injury, defined as the immediate effects of an injury to the spinal cord, and a secondary progressive and self-propagating stage, characterized by multiple cascades of biochemical events in which oxidative stress is a critical component causing further tissue loss and dysfunction [3, 9–15].

The second stage is characterized by an increased formation of reactive oxygen species (ROS) and consequently by oxidative stress [16, 17]. Skeletal muscle atrophy, as well as general deconditioning, and sedentary lifestyle, commonly observed in people with SCI, can influence oxidative stress and antioxidant capacity [18, 19]. Antioxidant-based interventions have been suggested to alleviate oxidative stress and therefore to improve health in individuals with SCI [17, 20, 21].

In this context, bioactive compounds from Mediterranean diet [22, 23], as well as from beverages and food dressing [22, 24], have been proposed as hormetins, improving antioxidant defences by an hormetic mechanism mediated by the activation of the nuclear factor erythroid-derived 2 (Nrf2) antioxidant response element (ARE) pathway [22]. Many dietary components of the Mediterranean diet, such as culinary herbs and spices, as well as extra virgin olive oil (EVOO) are rich in bioactive phytochemicals [25]. Moreover, epigallocatechin-3-gallate (EGCG) from green tea, activating the Nrf2-ARE [26], is among the flavonoids suggested for treatment of SCI [23]. The aim of the present work is to review the hormetic effects of bioactive compounds from foods, beverages, and food dressing (olive oil, spices, and herbs) to reduce oxidative stress in patients with SCI.

2. Oxidative Stress in Spinal Cord Injury

Reactive nitrogen species (RNS) and ROS are produced continuously in the body, but an augmented production of ROS could exceed the capacity of the antioxidant defences (Figure 1), mediating in this way oxidative stress and subsequently oxidative damage [27, 28].

Superoxide ($O_2^{\bullet-}$), produced by the mitochondrial electron transport chain, the xanthine oxidase (XO), and the NADPH oxidase (NOX), reacts with nitric oxide (NO^*), produced by the nitric oxide synthase (NOS), to form peroxynitrite ($ONOO^-$) [27, 29]. $O_2^{\bullet-}$ can be converted to hydrogen peroxide (H_2O_2) by the superoxide dismutase (SOD). The isoforms of SOD include the copper(Cu)/zinc(Zn)-SOD localized in the cytosol and in the extracellular space and the manganese(Mn)-SOD localized in the mitochondria. In this context, Zn has an essential role as part of the antioxidant defence system. Little is known about the database on the Zn status and its time-dependent changes after SCI [30–33]. A predictive model for a long-term functional outcome was obtained analyzing Zn dynamics in 38 cervically injured SCI patients [32]. Heller and colleagues [33] investigated the dynamic alterations in serum Zn concentration during the first 72 h after injury in short intervals in order to identify the relationship between the early changes of the total Zn serum level and neurological impairment and patients' outcome. They found that the median Zn concentrations in the group with neurological impairment throw down within the first 9 h after injury stronger than those in patients with vertebral fractures without neurological impairment. They concluded that the outcome is related to early Zn concentration dynamics and may be considered a helpful diagnostic indicator for these patients. In fact, the changes in serum Zn levels allow an assessment of neurological impairment risk on the first day after trauma [33]. In this

regard, it was shown that Zn treatment promoted motor function recovery during the 28 days following SCI and it seems to be able to reduce ROS and enhance the antioxidant activity [34].

Despite the antioxidant effect of SOD, in the presence of iron, H_2O_2 can generate via Fenton reaction the highly reactive hydroxyl radical (HO^*), initiator of the lipid peroxidation.

Both catalase (CAT) and glutathione peroxidase (GPX) catalyze the conversion of H_2O_2 into water and oxygen [35]. Among endogenous antioxidants, the main enzymes are SOD, CAT, GPX, and glutathione reductase, while glutathione (GSH) and uric acid (UA) are the major nonenzymatic antioxidants [27] (Figure 1).

GSH acts as antioxidant by scavenging ROS through GPX and by the reversible oxidation to glutathione disulphide (GSSG). The latter is reduced to GSH by the glutathione reductase. On the other hand, although XO produces $O_2^{\bullet-}$, it catalyzes the conversion of xanthine to UA which can scavenge $O_2^{\bullet-}$ and HO^* and is the major antioxidant in body fluids and preserves neuronal viability in pre-clinical models of SCI [36]. GPX is a selenium- (Se-) dependent enzyme and it was shown that Se nanoparticles could reverse oxidative stress-induced SCI in rats [37]. Seelig et al. [38] recently compared Se, Cu, selenoprotein P, and ceruloplasmin levels in patients with traumatic SCI versus individuals with vertebral fractures without neurological impairment and found that Cu and Se levels at admission and Se and ceruloplasmin levels after 24 h were predictors for potential remission of SCI.

Among minerals, magnesium (Mg) is suspected to have a key role in the secondary injury phase. Low Mg serum levels within the first 7 days have been described to be correlated with high probability of neurological remission [39]. In particular, Mg appears to reduce the production of ROS and lipid peroxidation [40]. Markers of the lipid product of oxidation include 4-hydroxy-2-nonenal (HNE), alkenals, alkanals, and malondialdehyde (MDA) being the thiobarbituric acid-reactive substances (TBARS) and F2-isoprostanes (F2-IsoP) derived by the nonenzymatic oxidation of polyunsaturated fatty acids [27].

Acrolein, an aldehyde produced endogenously through lipid peroxidation implicated in SCI, is more reactive than the other HNE and induces glutathione depletion [41]. On the other hand, Bastani et al. [42] analyzed a wide panel of antioxidant and oxidative stress biomarkers to define the antioxidant status in patients with SCI. They found that the urinary F2-IsoP and some enzymes (NOX and XO) in the vastus lateralis biopsies increased in the subjects with SCI compared with the controls, whereas SOD decreased. Besides, ROS production and apoptotic signals increased 1 and 3 months after SCI, while mitochondrial complexes and the SOD-2 protein content decreased 12 months after SCI [43].

On the other hand, advanced oxidation protein products (AOPP) in plasma, cerebrospinal fluid, and the spinal cord of rats increased after SCI and triggered generation of ROS (by activating NOX), with consequent induction of the p38 mitogen-activated protein kinase (p38MAPK) and the

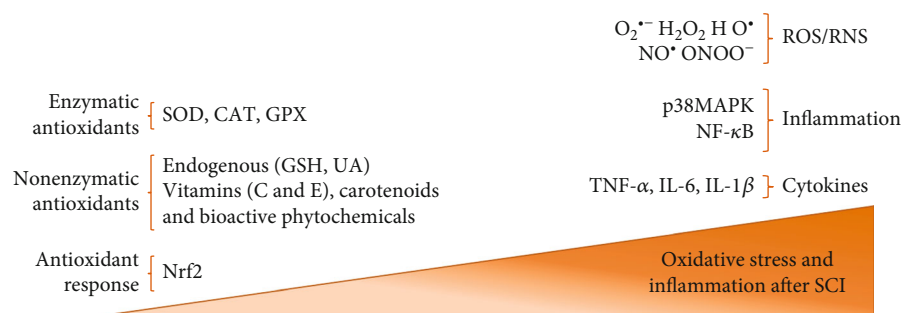


FIGURE 1: Representation of molecules involved in oxidative stress and inflammation after spinal cord injury (SCI). On the left are depicted the antioxidants that are present in low concentrations, while on the right are molecules that are present at higher levels causing oxidative stress. SOD: superoxide dismutase; CAT: catalase; GPX: glutathione peroxidase; GSH: glutathione; UA: uric acid; Nrf2: nuclear factor erythroid-derived 2; $O_2^{\bullet-}$: superoxide; H_2O_2 : hydrogen peroxide; HO^{\bullet} : hydroxyl radical; NO^{\bullet} : nitric oxide; $ONOO^-$: peroxynitrite; p38MAPK: p38 mitogen-activated protein kinase; $NF-\kappa B$: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF: tumor necrosis factor; IL: interleukin.

downstream regulated pathway nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells ($NF-\kappa B$) and proinflammatory cytokines [44]. AOPP include protein aggregates by disulphide bridges, as well as advanced peroxidation end products and advanced glycation end products. Other markers of protein oxidation include carbonyls [45] and the derivative of tyrosine from the reaction with the hypochlorous acid (HClO), generated by the H_2O_2 -dependent reaction catalyzed by the myeloperoxidase (MPO) or with $ONOO^-$ being 3-nitro-tyrosine as the main product of tyrosine oxidation [27]. Cysteine is particularly sensitive to oxidation and the reaction with NO^{\bullet} produces S-nitrosylated cysteine, whereas in the presence of a proximal thiol group, ROS damage results in the formation of a disulfide bond [27]. Oxidation of cysteine residues could be an essential feature for signaling pathways, including Nrf2/ARE.

3. Dietary Antioxidants in Spinal Cord Injury

The dietary advice for individuals with SCI included Mediterranean diet [46] and an anti-inflammatory diet [47]. The latter was able to increase (after 3 months) the intake of vitamins C (ascorbic acid) and E (alpha-tocopherol) in individuals with SCI, where proinflammatory markers were negatively correlated with carotenoids [47]. Patients with this condition (from at least 2 years) showed lower serum levels of these vitamins [48] and of vitamin E and beta-carotene [49], compared with healthy controls. Vitamins (C and E) and several bioactive compounds (such as carotenoids, phenolic compounds, and glucosinolates) are exogenous antioxidants that account for the antioxidant capacity of dietary sources (Table 1).

In 1991, an innovative study, subsequently confirmed in [54, 55], proved for the first time that rats treated with vitamin E were protected against induced muscle atrophy [56]. Nevertheless, this protection seemed to be due to the down-regulation of genes involved in the proteolysis of muscles, rather than by the antioxidant properties of vitamin E [57]. It has been reported that an improved bladder recovery and locomotor function in rats is associated with vitamin E-enriched diet. In fact, in order to improve sensory and auto-

nomic dysfunctions associated with SCI, the potential use of vitamin E was suggested [58]. Moreover, vitamin E treatment markedly enhanced the hind limb locomotor function, reduced the histopathological alterations and the morphological damage in the spinal cord, and the lowered MDA level and GPX activity in SCI [59]. On the contrary, combined treatment of vitamins C and E significantly contrasted the effects of spinal cord contusion on oxidative stress, increasing SOD and GPX [60]. Recently, synergistic effects of vitamin C and taurine against SCI in rats have been investigated and the combined treatment decreased mRNA expression of interleukin- (IL-) 6, cyclooxygenase- (COX-) 2, tumor necrosis factor- (TNF-) α , and inducible NOS (iNOS) compared to the single treatments and recovered altered antioxidant markers [61]. Moreover, vitamin C treatment alone suppressed $NF-\kappa B$, COX-2, and iNOS expressions in renal tissue, reduced the inflammatory responses (TNF- α and IL-1 β) and oxidative stress (TBARS, protein carbonyl, and MPO), and enhanced the antioxidant status (GSH, SOD, CAT, and GPX) after SCI-induced kidney damage [62]. On the other hand, the lipid-soluble plant pigments carotenoids, having antioxidant activity, have been suggested as neuroprotective nutraceuticals [63, 64]. The carotenoid lycopene found richly in red fruits and vegetables, due to its lipophilic structure, can pass through the blood-brain barrier and reach the brain [63]. It was demonstrated that lycopene treatment in SCI rats significantly improved oxidative stress, by reversing SOD, GPX, and MDA alterations [65]. Lycopene reduced lipid peroxidation in murine models [65, 66] and $NF-\kappa B$ activation in a mouse model of SCI [66]. Similar inhibition of $NF-\kappa B$ has been reported for beta-carotene in a rat model of SCI [67]. In particular, astaxanthin, crocetin, and lycopene decreased pain [68–72]. Moreover, astaxanthin [71], crocetin [73] and crocin improved locomotor function [74].

Among flavonoids, a study conducted in mice by Borghi et al. [75] showed that quercetin could be useful to treat muscle pain conditions linked to unaccustomed exercise due to its capacity to inhibit spinal cord cytokine production, oxidative stress, and glial cell activation. Furthermore, an experimental study conducted in rats by Ocal et al. [76] suggested that quercetin can be thought as an option of treatment in

TABLE 1: Some common sources of antioxidants of the Mediterranean diet.

	Glucosinolates (mg/100 g)	Vitamin C (mg/100 g)	Vitamin E (mg/100 g)	Retinol equivalents (μ g/100 g)	Beta-carotene (μ g/100 g)	Total phenolics* (mg/100 g)
Broccoli	61.7	77	1.3	123	738	89
Brussels sprouts	236.6	81	1.0	220	1320	221
Cabbage	58.9	47	0.18	19	738	81.73
Cauliflower	43.2	59	0.15	50	114	88.63
EVOO	—	—	22.4	36	—	55.14
Garlic	—	9	—	1	6.9	87.04
Kale	100.7	110	2.24	225	1350	176.67
Onion	—	5	0.22	3	0	69.49
Parsley	—	162	1.29	943	5658	836.9
Radish	92.5	18	0	0	0	44.3
Rosemary	—	29	1.5	92	550	1212.3
Sage leaves	—	0	9.15	215	3540	1049.3
Turnip	93.0	23	2.44	0	1794	93.5

*Folin assay. Data from [50–53].

SCI. Quercetin [77] and the citrus flavonoid hesperidin [78] exerted an anti-inflammatory effect. Several studies showed that the administration of the stilbene resveratrol after SCI could provide a beneficial impact on the neurological recovery and the antioxidant activity in rats [79–83], and a recent meta-analysis of studies in rat models of SCI revealed that it increased SOD and decreased MDA levels, compared to the control group [84].

The food dressing-derived bioactive compound rosmarinic acid, identified in rosemary (987 mg/100 g) from which its name derives [25], has been suggested for SCI in a recent review [85], whereas antioxidant and/or anti-inflammatory activities in murine models of SCI have been reported for curcumin [86–88] and oleanolic acid [89].

4. The Nuclear Erythroid 2-Related Factor 2 as the Target for Spinal Cord Injury Treatment

Nrf2 is a transcription factor that regulates the antioxidant response system and inhibits oxidative stress-mediated NF- κ B activation by decreasing the intracellular ROS levels [90, 91]. Normally, Nrf-2 is localized into the cytoplasm bound to the Kelch-like ECH-associating protein 1 (Keap1) that contains cysteine residues sensitive to oxidants or electrophiles [27]. Upon oxidation, Keap1 forms a disulfide bond and the conformational change results in the release of Nrf-2, allowing its translocation into the nucleus. Nrf-2 promotes the transcription of target genes containing the ARE in their promoter regions, including antioxidant enzymes and heme oxygenase 1 (HO-1). HO-1 is among the Nrf2-induced genes that inhibit NF- κ B activation [90, 91]. NF- κ B is normally sequestered inactive in the cytoplasm of resting cells by the inhibitor κ B (I κ B). The phosphorylation of two serines of I κ B, by the I κ B kinase (IKK), and its subsequent degradation by proteasome allow the activation of NF- κ B and its translocation to the nucleus [90, 91]. After nuclear translocation, NF- κ B induces the expression of proinflammatory cytokines,

as well as of ROS-producing enzymes, including COX-2 and iNOS [91]. Increasing levels of TNF- α , IL-6, COX-2, and iNOS activate the Nrf2/HO-1 axis that subsequently decreases their own expressions [91]. In addition, upregulation of Nrf2 reduces the I κ B- α proteasomal degradation and inhibits nuclear translocation of NF- κ B [91]. NF- κ B decreases the free CREB-binding protein (CBP also known as CREBBP), which is a transcriptional coactivator of Nrf2 by competing with CBP [91].

On the other hand, antioxidants with electrophilic moieties induce the Nrf2-mediated gene expression of antioxidant enzymes acting as prooxidants rather than antioxidants [26, 27, 92]. Besides, electrophilic modifications of cysteine 179 of IKK inhibit NF- κ B activation and have been suggested as one of the mechanisms involved in the anti-inflammatory effects of nutraceuticals [27, 92]. Therefore, Nrf2 has a fundamental role in the hormetic effect of natural bioactive compounds (Figure 2) and its signal pathway crosstalk with the NF- κ B pathway in animal models of SCI [93].

Hormetins typical of Mediterranean diet include molecules that interact with these transcription factors, such as vitamin E and many phytochemicals (terpenoids, phenolic antioxidants, allium-derived sulfur compounds, carotenoids, and resveratrol) from grapes, fruits, tomatoes, leafy green vegetables, legumes, onion, garlic, olives [22], and EVOO [94]. On the other hand, nonnutrient phytochemicals from spices often used for culinary purposes, namely, curcumin and ginger, as well as herb extracts (green tea extract, ginseng-based steroids, and ginsenosides) showed the capability to improve both oxidative stress and the inflammatory status in humans [92]. Some of these have been studied as bioactive molecules potentially useful against neurodegenerative diseases such as SCI [95].

Curcumin increased SOD levels [96] and decreased MDA [96] and proinflammatory cytokines, like TNF- α and IL-1 [97], and exerted its neuroprotective effect through the crosstalk between NF- κ B and Nrf2 signaling pathways [97].

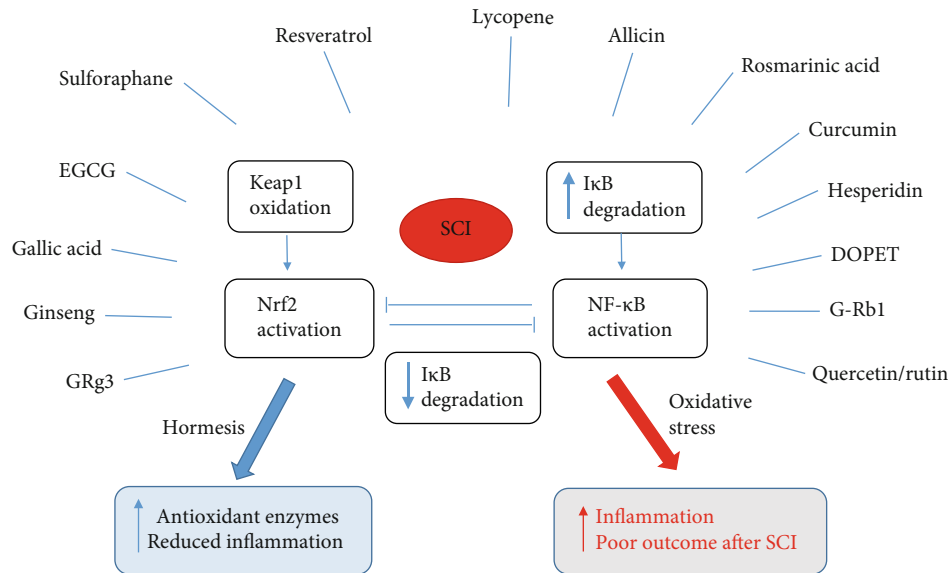


FIGURE 2: Bioactive compounds that act on the Nrf2/NF- κ B pathway. DOPET: 3,4-dihydroxyphenylethanol; EGCG: epigallocatechin-3-gallate; GR: ginsenoside R; I κ B: inhibitor κ B; Keap1: Kelch-like ECH-associating protein 1; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2: nuclear factor erythroid-derived 2; SCI: spinal cord injury.

Similar effects on the NF- κ B/Nrf2 pathway have been reported for sulforaphane, an isothiocyanate derived from broccoli, that is a potent naturally occurring inducer of the Keap1/Nrf2/ARE pathway and could mitigate inflammation through the inhibition of the NF- κ B pathway [98]. Also, EGCG from green tea induces the Keap1/Nrf2/ARE pathway [26]. To investigate neuroprotective potential of green tea polyphenols, Zhao et al. [99] induced oxidative damage in spinal cord neurons using H₂O₂ and applied different concentrations of green tea polyphenols to the cell medium for 24 hours. Measurements of SOD activity and MDA content revealed that green tea polyphenols reduced oxidative stress [99].

Ginseng treatment significantly downregulated inflammatory markers and oxidative stress by enhancing the antioxidant status in SCI rats [100]. In particular, ginsenoside R (GR) b1 attenuates SCI-associated oxidative stress in rats by regulating the endothelial NOS/Nrf2/HO-1 signaling pathway and increased SOD, CAT, and GSH [101], whereas GR g3 show anti-inflammatory, antioxidant, and neuroprotective effects, suppressing mRNA expression of proinflammatory cytokines (TNF- α , IL-1 β , and IL-6) and the overproduction of COX-2 and iNOS after SCI [102]. Reductions of COX-2 and NF- κ B expression have been observed also with gallic acid [103], a phenolic acid contained in various plant-food sources [53]. Hesperidin, a representative flavonoid in citrus fruits, reduced proinflammatory cytokines including TNF- α and IL-1 β , whereas it increased SOD, CAT, Nrf2, and HO-1 [104].

It was shown that resveratrol treatment suppressed the activation of the iNOS/p38MAPK pathway and reduced oxidative stress by enhancing enzymatic and nonenzymatic antioxidant levels such as those of GSH, SOD, and CAT in spinal cord ischemia-reperfusion injury-induced rats [105]. Furthermore, resveratrol showed a neuroprotective effect by increasing the activation of Nrf2 [106]. Preclinical studies

showed that the administration of resveratrol in the acute phase or prior to experimental injury to the central nervous system could have a neuroprotective [107]. Similar results were demonstrated for quercetin. In fact, in SCI rats, quercetin has protective effects on the spinal cord by the potential mechanism of inhibiting the activation of the iNOS/p38-MAPK signaling pathway and thus regulating secondary oxidative stress [108]. Quercetin treatment reversed MDA, NO, MPO, and cytokine levels and banned the exhaustion of tissue GSH levels and SOD [109]. Also, the quercetin-3-O-rutinoside (rutin) exerts neuroprotective effects through anti-inflammatory inhibition of the p38MAPK pathway [110]. A good source of quercetin is onion [53], and among bioactive compounds from Mediterranean food dressing, there are also rosmarinic acid, allicin, and 3,4-dihydroxyphenylethanol (DOPET).

Rosmarinic acid is a water-soluble polyphenolic phytochemical that could enhance the antioxidant status and consequently decrease the oxidative stress in Wistar rats post-SCI by targeting Nrf2/HO-1 and NF- κ B pathways, downregulating proinflammatory cytokines (TNF- α , IL-6, and IL-1 β), and acting as neuroprotective agent [111, 112].

Garlic and onion are rich in organosulfur compounds, including allium and allicin, that induce the Nrf2 pathway [22]. Allicin, the main biologically active compound derived from garlic, seems to have neuroprotective effects in animal models, being able to increase the activities of antioxidant enzymes, including CAT, SOD, GPX, and glutathione S-transferase [113]. In addition, it was shown that allicin enhanced the motor functional recovery and increased Nrf2 nuclear expression [114], while it decreased the expression of inducible NOS but had no effects on the expression of neuronal NOS following glutamate exposure [115].

DOPET is a potent antioxidant polyphenolic compound from EVOO targeting multiple signaling pathways to reduce

SCI effects, including reduction of MPO and downregulation of proinflammatory cytokines [116]. Moreover, it has been previously reviewed that other bioactive compounds of EVOO, such as hydroxytyrosol [22, 94] and oleuropein [22], can activate the Nrf2 pathway, but specific studies are needed on SCI. Transcription of antioxidant genes mediated by Nrf2 could be also enhanced by ferulic acid (present in fruit, tomatoes, and rice), luteolin (present in carrots, peppers, and celery), phenethyl isothiocyanate (present in crucifer vegetables), and carnolic acid (abundant in rosemary) [22]. Therefore, many bioactive compounds should be tested in SCI in future studies.

5. Conclusion

SCI results, since the early stages, in an imbalance between the ROS production and antioxidant defences (Figure 1). Low levels of some micronutrients, including antioxidant vitamins and minerals involved in antioxidant enzymes' activity, have been reported in individuals with SCI. ESPEN guidelines suggested supplementation with antioxidant micronutrients for patients in the intensive care unit [117] and with neurological diseases [118] and reported in an observational study that this is practiced also in individuals with cervical SCI [119].

Dietary advice and supplements have been proposed in order to reduce oxidative stress, and in some cases, synergistic effects have been reported. Although curcumin, ginseng, and green tea have been proposed for SCI management, low levels of antioxidant vitamins have been reported in individuals with SCI. Mediterranean diet that includes food, spices, and herbs contains multiple components with antioxidant properties (Table 1), such as vitamins, phenolic compounds, and glucosinolates. The latter are known to activate Nrf2 by an electrophilic interaction with sulfhydryl-groups on Keap1, therefore in a hormetic manner. Oxidation of cysteine residue of Keap1 is involved in the EGCG induction of Nrf2. On the other hand, nonnutrient bioactive compounds from food, spices, and herbs typical of the Mediterranean diet could reduce oxidative stress by activating the Nrf2 pathway, acting as hormetins. Although many of these compounds have low bioavailability, hormetic effects typically occur at low concentration. Moreover, nanoparticle-based formulations have been suggested to improve bioavailability of flavonoids [120] and carotenoids [121] and resveratrol efficacy in SCI [122]. In particular, rats with SCI treated with resveratrol- and puerarin-loaded nanoparticles showed a decrease of GSH, SOD, and CAT antioxidant levels [122]. On the other hand, squalene from EVOO has been suggested as natural delivery system for bioactive compounds [123]. It was observed that carotenoids' absorption was higher in people that consumed salads with full-fat dressing [124]. Furthermore, EVOO is a source of vitamin E and contains many bioactive compounds [22]. From that, Mediterranean dressing in addition to plant foods can have an important effect on the redox balance in individuals with SCI. From a clinical point of view, this evidence could support the patients during both the early rehabilitation phases and the chronic management. In conclusion, the previously

suggested hormetic effects of Mediterranean diet [22] that can be considered a natural multicomponent supplement [125] could be useful for the long-term management of SCI.

Abbreviations

AOPP:	Advanced oxidation protein products
ARE:	Antioxidant response elements
CAT:	Catalase
COX:	Cyclooxygenase
Cu:	Copper
DOPET:	3,4-Dihydroxyphenylethanol
EGCG:	Epigallocatechin-3-gallate
EVOO:	Extra virgin olive oil
F2-isoP:	F2 isoprostanes
GPX:	Glutathione peroxidase
GR:	Ginsenoside R
GSH:	Glutathione
GSSG:	Glutathione disulphide
H ₂ O ₂ :	Hydrogen peroxide
HClO:	Hypochlorous acid
HNE:	4-Hydroxy-2-nonenal
HO:	Heme oxygenase
HO•:	Hydroxyl radical
IL:	Interleukin
IκB:	Inhibitor κB
IKK:	IκB kinase
iNOS:	Inducible NOS
Keap1:	Kelch-like ECH-associating protein 1
MAPK:	Mitogen-activated protein kinase
MDA:	Malondialdehyde
Mg:	Magnesium
Mn:	Manganese
MPO:	Myeloperoxidase
NF-κB:	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO•:	Nitric oxide
NOS:	Nitric oxide synthase
NOX:	NADPH oxidase
Nrf2:	Nuclear factor erythroid-derived 2
O ₂ ^{•-} :	Superoxide
ONOO ⁻ :	Peroxynitrite
RNS:	Reactive nitrogen species
ROS:	Reactive oxygen species
SCI:	Spinal cord injury
Se:	Selenium
SOD:	Superoxide dismutase
TBARS:	Thiobarbituric acid-reactive substances
TNF:	Tumor necrosis factor
UA:	Uric acid
XO:	Xanthine oxidase
Zn:	Zinc.

Disclosure

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sedentary lifestyle, physical activity, and dietary habits (CISAFAL).

Conflicts of Interest

The authors declare no conflict of interest.

References

- [1] C. S. Ahuja, J. R. Wilson, S. Nori et al., "Traumatic spinal cord injury," *Nature Reviews. Disease Primers*, vol. 3, no. 1, article 17018, 2017.
- [2] P. W. New and F. Biering-Sorensen, "Review of the history of non-traumatic spinal cord dysfunction," *Topics in Spinal Cord Injury Rehabilitation*, vol. 23, no. 4, pp. 285–298, 2017.
- [3] C. Carrasco, M. Naziroglu, A. B. Rodriguez, and J. A. Pariente, "Neuropathic pain: delving into the oxidative origin and the possible implication of transient receptor potential channels," *Frontiers in Physiology*, vol. 9, p. 95, 2018.
- [4] S. C. Kirshblum, S. P. Burns, F. Biering-Sorensen et al., "International standards for neurological classification of spinal cord injury (revised 2011)," *The Journal of Spinal Cord Medicine*, vol. 34, no. 6, pp. 535–546, 2013.
- [5] M. Committee, S. Burns, F. Biering-Sorensen et al., "International standards for neurological classification of spinal cord injury, revised 2011," *Topics in Spinal Cord Injury Rehabilitation*, vol. 18, no. 1, pp. 85–99, 2012.
- [6] S. Kirshblum and W. Waring 3rd, "Updates for the international standards for neurological classification of spinal cord injury," *Physical Medicine and Rehabilitation Clinics of North America*, vol. 25, no. 3, pp. 505–517, 2014, vii.
- [7] Asia and I S I S Committee, "The 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)—What's new?," *Spinal Cord*, vol. 57, no. 10, pp. 815–817, 2019.
- [8] C. Schuld, S. Franz, K. Bruggemann et al., "international standards for neurological classification of spinal cord injury: impact of the revised worksheet (revision 02/13) on classification performance," *The Journal of Spinal Cord Medicine*, vol. 39, no. 5, pp. 504–512, 2016.
- [9] E. Hayta and H. Elden, "Acute spinal cord injury: a review of pathophysiology and potential of non-steroidal anti-inflammatory drugs for pharmacological intervention," *Journal of Chemical Neuroanatomy*, vol. 87, pp. 25–31, 2018.
- [10] C. A. Oyinbo, "Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade," *Acta Neurobiologiae Experimentalis (Wars)*, vol. 71, no. 2, pp. 281–299, 2011.
- [11] R. E. von Leden, Y. J. Yauger, G. Khayrullina, and K. R. Byrnes, "Central nervous system injury and nicotinamide adenine dinucleotide phosphate oxidase: oxidative stress and therapeutic targets," *Journal of Neurotrauma*, vol. 34, no. 4, pp. 755–764, 2017.
- [12] A. P. Tran, P. M. Warren, and J. Silver, "The biology of regeneration failure and success after spinal cord injury," *Physiological Reviews*, vol. 98, no. 2, pp. 881–917, 2018.
- [13] S. M. Dyck and S. Karimi-Abdolrezaee, "Chondroitin sulfate proteoglycans: key modulators in the developing and pathologic central nervous system," *Experimental Neurology*, vol. 269, pp. 169–187, 2015.
- [14] A. Alizadeh and S. Karimi-Abdolrezaee, "Microenvironmental regulation of oligodendrocyte replacement and remyelination in spinal cord injury," *The Journal of Physiology*, vol. 594, no. 13, pp. 3539–3552, 2016.
- [15] A. Alizadeh, S. M. Dyck, and S. Karimi-Abdolrezaee, "Myelin damage and repair in pathologic CNS: challenges and prospects," *Frontiers in Molecular Neuroscience*, vol. 8, p. 35, 2015.
- [16] A. Anjum, M. D. Yazid, M. Fauzi Daud et al., "Spinal cord injury: pathophysiology, multimolecular interactions, and underlying recovery mechanisms," *International Journal of Molecular Sciences*, vol. 21, no. 20, p. 7533, 2020.
- [17] Z. Jia, H. Zhu, J. Li, X. Wang, H. Misra, and Y. Li, "Oxidative stress in spinal cord injury and antioxidant-based intervention," *Spinal Cord*, vol. 50, no. 4, pp. 264–274, 2012.
- [18] W. Qin, W. A. Bauman, and C. Cardozo, "Bone and muscle loss after spinal cord injury: organ interactions," *Annals of the New York Academy of Sciences*, vol. 1211, no. 1, pp. 66–84, 2010.
- [19] G. Fatima, V. P. Sharma, S. K. Das, and A. A. Mahdi, "Oxidative stress and antioxidative parameters in patients with spinal cord injury: implications in the pathogenesis of disease," *Spinal Cord*, vol. 53, no. 1, pp. 3–6, 2015.
- [20] M. Bains and E. D. Hall, "Antioxidant therapies in traumatic brain and spinal cord injury," *Biochimica et Biophysica Acta*, vol. 1822, no. 5, pp. 675–684, 2012.
- [21] E. D. Hall, "Antioxidant therapies for acute spinal cord injury," *Neurotherapeutics*, vol. 8, no. 2, pp. 152–167, 2011.
- [22] M. Martucci, R. Ostan, F. Biondi et al., "Mediterranean diet and inflammaging within the hormesis paradigm," *Nutrition Reviews*, vol. 75, no. 6, pp. 442–455, 2017.
- [23] A. Coyoy-Salgado, J. J. Segura-Urbe, C. Guerra-Araiza et al., "The importance of natural antioxidants in the treatment of spinal cord injury in animal models: an overview," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 3642491, 22 pages, 2019.
- [24] A. B. Kunnumakkara, D. Bordoloi, G. Padmavathi et al., "Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases," *British Journal of Pharmacology*, vol. 174, no. 11, pp. 1325–1348, 2017.
- [25] M. Issaoui, A. M. Delgado, G. Caruso et al., "Phenols, flavors, and the Mediterranean diet," *Journal of AOAC International*, vol. 103, no. 4, pp. 915–924, 2020.
- [26] M. Serafini, D. Del Rio, D. N. Yao, S. Bettuzzi, and I. Peluso, "Health Benefits of Tea," in *Herbal Medicine: Biomolecular and Clinical Aspects*, I. F. F. Benzie and S. Wachtel-Galor, Eds., CRC Press/Taylor & Francis, Boca Raton (FL), 2011, <http://www.ncbi.nlm.nih.gov/pubmed/22593935>.
- [27] I. Marrocco, F. Altieri, and I. Peluso, "Measurement and clinical significance of biomarkers of oxidative stress in humans," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 6501046, 32 pages, 2017.
- [28] O. Campuzano, M. M. Castillo-Ruiz, L. Acarin, B. Gonzalez, and B. Castellano, "Decreased myeloperoxidase expressing cells in the aged rat brain after excitotoxic damage," *Experimental Gerontology*, vol. 46, no. 9, pp. 723–730, 2011.
- [29] I. Peluso, G. Morabito, L. Urban, F. Ioannone, and M. Serafi, "Oxidative stress in atherosclerosis development: the central role of LDL and oxidative burst," *Endocrine, Metabolic & Immune Disorders - Drug Targets*, vol. 12, no. 4, pp. 351–360, 2012.

- [30] A. C. Lynch, C. Palmer, A. C. Lynch et al., “Nutritional and immune status following spinal cord injury: a case controlled study,” *Spinal Cord*, vol. 40, no. 12, pp. 627–630, 2002.
- [31] G. J. Farkas, M. A. Pitot, A. S. Berg, and D. R. Gater, “Nutritional status in chronic spinal cord injury: a systematic review and meta-analysis,” *Spinal Cord*, vol. 57, no. 1, pp. 3–17, 2019.
- [32] K. Kijima, K. Kubota, M. Hara et al., “The acute phase serum zinc concentration is a reliable biomarker for predicting the functional outcome after spinal cord injury,” *eBioMedicine*, vol. 41, pp. 659–669, 2019.
- [33] R. A. Heller, A. Sperl, J. Seelig et al., “Zinc concentration dynamics indicate neurological impairment odds after traumatic spinal cord injury,” *Antioxidants (Basel)*, vol. 9, no. 5, p. 421, 2020.
- [34] D. Li, H. Tian, X. Li et al., “Zinc promotes functional recovery after spinal cord injury by activating Nrf2/HO-1 defense pathway and inhibiting inflammation of NLRP3 in nerve cells,” *Life Sciences*, vol. 245, p. 117351, 2020.
- [35] E. D. Hall, J. A. Wang, J. M. Bosken, and I. N. Singh, “Lipid peroxidation in brain or spinal cord mitochondria after injury,” *Journal of Bioenergetics and Biomembranes*, vol. 48, no. 2, pp. 169–174, 2016.
- [36] N. K. Singh, S. Khaliq, M. Patel et al., “Uric acid released from poly(ϵ -caprolactone) fibers as a treatment platform for spinal cord injury,” *Journal of Tissue Engineering and Regenerative Medicine*, vol. 15, no. 1, pp. 14–23, 2021.
- [37] S. Rao, Y. Lin, Y. Du et al., “Designing multifunctionalized selenium nanoparticles to reverse oxidative stress-induced spinal cord injury by attenuating ROS overproduction and mitochondria dysfunction,” *Journal of Materials Chemistry B*, vol. 7, no. 16, pp. 2648–2656, 2019.
- [38] J. Seelig, R. A. Heller, J. Hackler et al., “Selenium and copper status - potential signposts for neurological remission after traumatic spinal cord injury,” *Journal of Trace Elements in Medicine and Biology*, vol. 57, p. 126415, 2020.
- [39] A. Sperl, R. A. Heller, B. Biglari et al., “The Role of Magnesium in the Secondary Phase After Traumatic Spinal Cord Injury. A Prospective Clinical Observer Study,” *Antioxidants (Basel)*, vol. 8, no. 11, p. 509, 2019.
- [40] N. L. Cook, F. Corrigan, and C. van den Heuvel, “The role of magnesium in CNS injury,” in *Magnesium in the Central Nervous System*, R. Vink and M. Nechifor, Eds., University of Adelaide Press, Adelaide (AU), 2011.
- [41] R. Shi, T. Rickett, and W. Sun, “Acrolein-mediated injury in nervous system trauma and diseases,” *Molecular Nutrition & Food Research*, vol. 55, no. 9, pp. 1320–1331, 2011.
- [42] N. E. Bastani, E. Kostovski, A. K. Sakhi et al., “Reduced antioxidant defense and increased oxidative stress in spinal cord injured patients,” *Archives of Physical Medicine and Rehabilitation*, vol. 93, no. 12, pp. 2223–2228.e2, 2012, e2.
- [43] M. Savikj, E. Kostovski, L. S. Lundell, P. O. Iversen, J. Massart, and U. Widgren, “Altered oxidative stress and antioxidant defence in skeletal muscle during the first year following spinal cord injury,” *Physiological Reports*, vol. 7, no. 16, article e14218, 2019.
- [44] Z. Liu, X. Yao, W. Jiang et al., “Advanced oxidation protein products induce microglia-mediated neuroinflammation via MAPKs-NF- κ B signaling pathway and pyroptosis after secondary spinal cord injury,” *Journal of Neuroinflammation*, vol. 17, no. 1, p. 90, 2020.
- [45] F. J. Ordonez, M. A. Rosety, A. Camacho et al., “Arm-anking exercise reduced oxidative damage in adults with chronic spinal cord injury,” *Archives of Physical Medicine and Rehabilitation*, vol. 94, no. 12, pp. 2336–2341, 2013.
- [46] M. Bernardi, A. L. Fedullo, E. Bernardi et al., “Diet in neurogenic bowel management: a viewpoint on spinal cord injury,” *World Journal of Gastroenterology*, vol. 26, no. 20, pp. 2479–2497, 2020.
- [47] D. J. Allison, K. M. Beaudry, A. M. Thomas, A. R. Josse, and D. S. Ditor, “Changes in nutrient intake and inflammation following an anti-inflammatory diet in spinal cord injury,” *The Journal of Spinal Cord Medicine*, vol. 42, no. 6, pp. 768–777, 2019.
- [48] R. M. Moussavi, H. M. Garza, S. G. Eisele, G. Rodriguez, and D. H. Rintala, “Serum levels of vitamins A, C, and E in persons with chronic spinal cord injury living in the community1,” *Archives of Physical Medicine and Rehabilitation*, vol. 84, no. 7, pp. 1061–1067, 2003.
- [49] B. J. Burri, M. Dopler-Nelson, and T. R. Neidlinger, “Measurements of the major isoforms of vitamins A and E and carotenoids in the blood of people with spinal-cord injuries,” *Journal of Chromatography. A*, vol. 987, no. 1-2, pp. 359–366, 2003.
- [50] S. A. McNaughton and G. C. Marks, “Development of a food composition database for the estimation of dietary intakes of glucosinolates, the biologically active constituents of cruciferous vegetables,” *The British Journal of Nutrition*, vol. 90, no. 3, pp. 687–697, 2003.
- [51] CREA-AN, “Tabelle di Composizione degli Alimenti,” <https://www.crea.gov.it/-/tabella-di-composizione-degli-alimenti>.
- [52] USDA, “Food Composition Database,” <https://www.nal.usda.gov/usda-food-composition-database>.
- [53] Phenol-Explorer, “Comprehensive database on polyphenol content in foods,” <http://phenol-explorer.eu/>.
- [54] L. L. Blythe, A. M. Craig, E. D. Lassen, K. E. Rowe, and L. H. Appell, “Serially determined plasma alpha-tocopherol concentrations and results of the oral vitamin E absorption test in clinically normal horses and in horses with degenerative myeloencephalopathy,” *American Journal of Veterinary Research*, vol. 52, no. 6, pp. 908–911, 1991.
- [55] S. Demiryurek and A. Babul, “Effects of vitamin E and electrical stimulation on the denervated rat gastrocnemius muscle malondialdehyde and glutathione levels,” *The International Journal of Neuroscience*, vol. 114, no. 1, pp. 45–54, 2009.
- [56] H. Kondo, M. Miura, and Y. Itokawa, “Oxidative stress in skeletal muscle atrophied by immobilization,” *Acta Physiologica Scandinavica*, vol. 142, no. 4, pp. 527–528, 1991.
- [57] S. Servais, D. Letexier, R. Favier, C. Duchamp, and D. Desplanches, “Prevention of unloading-induced atrophy by vitamin E supplementation: links between oxidative stress and soleus muscle proteolysis?,” *Free Radical Biology & Medicine*, vol. 42, no. 5, pp. 627–635, 2007.
- [58] K. Cordero, G. Coronel, M. Serrano-Illán, J. Cruz-Bracero, J. Figueroa, and M. De León, “Effects of dietary vitamin E supplementation in bladder function and spasticity during spinal cord injury,” *Brain Sciences*, vol. 8, no. 3, p. 38, 2018.
- [59] P. M. Zadeh-Ardabili, S. K. Rad, S. K. Rad, H. Khazaai, J. Sanusi, and M. H. Zadeh, “Palm vitamin E reduces locomotor dysfunction and morphological changes induced by

- spinal cord injury and protects against oxidative damage,” *Scientific Reports*, vol. 7, no. 1, p. 14365, 2017.
- [60] H. C. Chen, P. W. Hsu, W. C. Tzaan, and A. W. Lee, “Effects of the combined administration of vitamins C and E on the oxidative stress status and programmed cell death pathways after experimental spinal cord injury,” *Spinal Cord*, vol. 52, no. 1, pp. 24–28, 2014.
- [61] C. Chen, Q. Yang, and X. Ma, “Synergistic effect of ascorbic acid and taurine in the treatment of a spinal cord injury-induced model in rats,” *3 Biotech*, vol. 10, no. 2, p. 50, 2020.
- [62] W. G. Wang, R. J. Xiu, Z. W. Xu et al., “Protective effects of vitamin C against spinal cord injury-induced renal damage through suppression of NF- κ B and proinflammatory cytokines,” *Neurological Sciences*, vol. 36, no. 4, pp. 521–526, 2015.
- [63] R. Paul, M. K. Mazumder, J. Nath et al., “Lycopene - a pleiotropic neuroprotective nutraceutical: deciphering its therapeutic potentials in broad spectrum neurological disorders,” *Neurochemistry International*, vol. 140, p. 104823, 2020.
- [64] S. Fakhri, I. Y. Aneva, M. H. Farzaei, and E. Sobarzo-Sanchez, “The neuroprotective effects of astaxanthin: therapeutic targets and clinical perspective,” *Molecules*, vol. 24, no. 14, p. 2640, 2019.
- [65] W. Hu, H. Wang, Z. Liu et al., “Neuroprotective effects of lycopene in spinal cord injury in rats via antioxidative and anti-apoptotic pathway,” *Neuroscience Letters*, vol. 642, pp. 107–112, 2017.
- [66] Q. Zhang, J. Wang, Z. Gu, Q. Zhang, and H. Zheng, “Effect of lycopene on the blood-spinal cord barrier after spinal cord injury in mice,” *Bioscience Trends*, vol. 10, no. 4, pp. 288–293, 2016.
- [67] L. Zhou, L. Ouyang, S. Lin et al., “Protective role of β -carotene against oxidative stress and neuroinflammation in a rat model of spinal cord injury,” *International Immunopharmacology*, vol. 61, pp. 92–99, 2018.
- [68] A. Masoudi, L. Dargahi, F. Abbaszadeh et al., “Neuroprotective effects of astaxanthin in a rat model of spinal cord injury,” *Behavioural Brain Research*, vol. 329, pp. 104–110, 2017.
- [69] X. Wang, G. Zhang, Y. Qiao, C. Feng, and X. Zhao, “Crocin attenuates spared nerve injury-induced neuropathic pain in mice,” *Journal of Pharmacological Sciences*, vol. 135, no. 4, pp. 141–147, 2017.
- [70] Y. Hua, N. Xu, T. Ma, Y. Liu, H. Xu, and Y. Lu, “Anti-inflammatory effect of lycopene on experimental spinal cord ischemia injury via cyclooxygenase-2 suppression,” *Neuroimmunomodulation*, vol. 26, no. 2, pp. 84–92, 2019.
- [71] S. Fakhri, L. Dargahi, F. Abbaszadeh, and M. Jorjani, “Effects of astaxanthin on sensory-motor function in a compression model of spinal cord injury: involvement of ERK and AKT signalling pathway,” *European Journal of Pain*, vol. 23, no. 4, pp. 750–764, 2019.
- [72] F. F. Zhang, N. Morioka, T. Kitamura et al., “Lycopene ameliorates neuropathic pain by upregulating spinal astrocytic connexin 43 expression,” *Life Sciences*, vol. 155, pp. 116–122, 2016.
- [73] X. Wang, X. Jiao, Z. Liu, and Y. Li, “Crocin potentiates neurite growth in hippocampal neurons and facilitates functional recovery in rats with spinal cord injury,” *Neuroscience Bulletin*, vol. 33, no. 6, pp. 695–702, 2017.
- [74] M. Karami, S. Z. Bathaie, T. Tiraihi, M. Habibi-Rezaei, J. Arabkheradmand, and S. Faghizadeh, “Crocin improved locomotor function and mechanical behavior in the rat model of contused spinal cord injury through decreasing calcitonin gene related peptide (CGRP),” *Phytomedicine*, vol. 21, no. 1, pp. 62–67, 2013.
- [75] S. M. Borghi, F. A. Pinho-Ribeiro, V. Fattori et al., “Quercetin inhibits peripheral and spinal cord nociceptive mechanisms to reduce intense acute swimming-induced muscle pain in mice,” *PLoS One*, vol. 11, no. 9, article e0162267, 2016.
- [76] O. Ocal, A. O. Borcek, O. Pasaoglu, A. C. Gundogdu, G. T. Kaplanoglu, and M. K. Baykaner, “Can quercetin be an option for treatment of spinal cord injury? An Experimental Study,” *Turkish Neurosurgery*, vol. 29, no. 2, pp. 247–253, 2018.
- [77] H. Fan, H. B. Tang, L. Q. Shan et al., “Quercetin prevents necroptosis of oligodendrocytes by inhibiting macrophages/microglia polarization to M1 phenotype after spinal cord injury in rats,” *Journal of Neuroinflammation*, vol. 16, no. 1, p. 206, 2019.
- [78] Z. Yurtal, M. E. Altug, E. Unsaldi, I. E. Secinti, and A. Kucukgul, “Investigation of Neuroprotective and Therapeutic Effect of Hesperidin in Experimental Spinal Cord Injury,” *Turkish Neurosurgery*, vol. 30, no. 6, pp. 899–906, 2020.
- [79] S. Zhang, B. O. A. Botchway, Y. Zhang, and X. Liu, “Resveratrol can inhibit Notch signaling pathway to improve spinal cord injury,” *Annals of Anatomy*, vol. 223, pp. 100–107, 2019.
- [80] X. Liu, B. O. A. Botchway, X. Tan, Y. Zhang, and M. Fang, “Resveratrol treatment of spinal cord injury in rat model,” *Microscopy Research and Technique*, vol. 82, no. 3, pp. 296–303, 2019.
- [81] L. Xu, B. O. A. Botchway, S. Zhang, J. Zhou, and X. Liu, “Inhibition of NF- κ B signaling pathway by resveratrol improves spinal cord injury,” *Frontiers in Neuroscience*, vol. 12, p. 690, 2018.
- [82] J. Zhou, X. Huo, B. O. A. Botchway et al., “Beneficial effects of resveratrol-mediated inhibition of the mTOR pathway in spinal cord injury,” *Neural Plasticity*, vol. 2018, Article ID 7513748, 8 pages, 2018.
- [83] H. Y. Meng, D. C. Shao, H. Li et al., “Resveratrol improves neurological outcome and neuroinflammation following spinal cord injury through enhancing autophagy involving the AMPK/mTOR pathway,” *Molecular Medicine Reports*, vol. 18, no. 2, pp. 2237–2244, 2018.
- [84] B. P. Xu, M. Yao, Z. J. Li et al., “Neurological recovery and antioxidant effects of resveratrol in rats with spinal cord injury: a meta-analysis,” *Neural Regeneration Research*, vol. 15, no. 3, pp. 482–490, 2020.
- [85] M. Ghasemzadeh Rahbardar and H. Hosseinzadeh, “Effects of rosmarinic acid on nervous system disorders: an updated review,” *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 393, no. 10, pp. 1779–1795, 2020.
- [86] B. G. Alvarado-Sanchez, H. Salgado-Ceballos, S. Torres-Castillo et al., “Electroacupuncture and curcumin promote oxidative balance and motor function recovery in rats following traumatic spinal cord injury,” *Neurochemical Research*, vol. 44, no. 2, pp. 498–506, 2019.
- [87] J. Yuan, B. O. A. Botchway, Y. Zhang, X. Tan, X. Wang, and X. Liu, “Curcumin can improve spinal cord injury by inhibiting TGF- β -SOX9 signaling pathway,” *Cellular and Molecular Neurobiology*, vol. 39, no. 5, pp. 569–575, 2019.
- [88] Y. S. Lee, D. C. Cho, C. H. Kim, I. Han, E. Y. Gil, and K. T. Kim, “Effect of curcumin on the inflammatory reaction and

- functional recovery after spinal cord injury in a hyperglycemic rat model,” *The Spine Journal*, vol. 19, no. 12, pp. 2025–2039, 2019.
- [89] J. L. Wang, C. H. Ren, J. Feng, C. H. Ou, and L. Liu, “Oleonic acid inhibits mouse spinal cord injury through suppressing inflammation and apoptosis via the blockage of p38 and JNK MAPKs,” *Biomedicine & Pharmacotherapy*, vol. 123, p. 109752, 2020.
- [90] I. Bellezza, A. L. Mierla, and A. Minelli, “Nrf2 and NF- κ B and their concerted modulation in cancer pathogenesis and progression,” *Cancers (Basel)*, vol. 2, no. 2, pp. 483–497, 2010.
- [91] S. Saha, B. Buttari, E. Panieri, E. Profumo, and L. Saso, “An overview of Nrf2 signaling pathway and its role in inflammation,” *Molecules*, vol. 25, no. 22, p. 5474, 2020.
- [92] M. Serafini and I. Peluso, “Functional foods for health: the interrelated antioxidant and anti-inflammatory role of fruits, vegetables, herbs, spices and cocoa in humans,” *Current Pharmaceutical Design*, vol. 22, no. 44, pp. 6701–6715, 2017.
- [93] S. Samarghandian, A. M. Pourbagher-Shahri, M. Ashrafzadeh et al., “A pivotal role of the Nrf2 signaling pathway in spinal cord injury: a prospective therapeutics study,” *CNS & Neurological Disorders Drug Targets*, vol. 19, no. 3, pp. 207–219, 2020.
- [94] M. Piroddi, A. Albini, R. Fabiani et al., “Nutrigenomics of extra-virgin olive oil: a review,” *BioFactors*, vol. 43, no. 1, pp. 17–41, 2017.
- [95] A. K. Kiani, G. A. D. Miggiano, B. Aquilanti et al., “Food supplements based on palmitoylethanolamide plus hydroxytyrosol from olive tree or Bacopa monnieri extracts for neurological diseases,” *Acta Biomed*, vol. 91, no. 13-S, article e2020007, 2020.
- [96] H. Sahin Kavakli, C. Koca, and O. Alici, “Antioxidant effects of curcumin in spinal cord injury in rats,” *Ulus Travma Acil Cerrahi Derg*, vol. 17, no. 1, pp. 14–18, 2011.
- [97] A. Daverey and S. K. Agrawal, “Curcumin protects against white matter injury through NF- κ B and Nrf2 cross talk,” *Journal of Neurotrauma*, vol. 37, no. 10, pp. 1255–1265, 2020.
- [98] A. L. Benedict, A. Mountney, A. Hurtado et al., “Neuroprotective effects of sulforaphane after contusive spinal cord injury,” *Journal of Neurotrauma*, vol. 29, no. 16, pp. 2576–2586, 2012.
- [99] P. Tang, X. Mei, J. Zhao et al., “Green tea polyphenols protect spinal cord neurons against hydrogen peroxide-induced oxidative stress,” *Neural Regeneration Research*, vol. 9, no. 14, pp. 1379–1385, 2014.
- [100] W. Wang, H. Shen, J. J. Xie, J. Ling, and H. Lu, “Neuroprotective effect of ginseng against spinal cord injury induced oxidative stress and inflammatory responses,” *International Journal of Clinical and Experimental Medicine*, vol. 8, no. 3, pp. 3514–3521, 2015.
- [101] X. Liu, X. Gu, M. Yu et al., “Effects of ginsenoside Rb1 on oxidative stress injury in rat spinal cords by regulating the eNOS/Nrf2/HO-1 signaling pathway,” *Experimental and Therapeutic Medicine*, vol. 16, no. 2, pp. 1079–1086, 2018.
- [102] D. K. Kim, K. J. Kweon, P. Kim et al., “Ginsenoside Rg3 improves recovery from spinal cord injury in rats via suppression of neuronal apoptosis, pro-inflammatory mediators, and microglial activation,” *Molecules*, vol. 22, no. 1, p. 122, 2017.
- [103] Y. H. Yang, Z. Wang, J. Zheng, and R. Wang, “Protective effects of gallic acid against spinal cord injury-induced oxidative stress,” *Molecular Medicine Reports*, vol. 12, no. 2, pp. 3017–3024, 2015.
- [104] S. D. Heo, J. Kim, Y. Choi, P. Ekanayake, M. Ahn, and T. Shin, “Hesperidin improves motor disability in rat spinal cord injury through anti-inflammatory and antioxidant mechanism via Nrf-2/HO-1 pathway,” *Neuroscience Letters*, vol. 715, p. 134619, 2020.
- [105] S. Fu, R. Lv, L. Wang, H. Hou, H. Liu, and S. Shao, “Resveratrol, an antioxidant, protects spinal cord injury in rats by suppressing MAPK pathway,” *Saudi Journal of Biological Sciences*, vol. 25, no. 2, pp. 259–266, 2018.
- [106] V. Kesharwani, F. Atif, S. Yousuf, and S. K. Agrawal, “Resveratrol protects spinal cord dorsal column from hypoxic injury by activating Nrf-2,” *Neuroscience*, vol. 241, pp. 80–88, 2013.
- [107] M. S. Lopez, R. J. Dempsey, and R. Vemuganti, “Resveratrol neuroprotection in stroke and traumatic CNS injury,” *Neurochemistry International*, vol. 89, pp. 75–82, 2015.
- [108] Y. Song, J. Liu, F. Zhang, J. Zhang, T. Shi, and Z. Zeng, “Antioxidant effect of quercetin against acute spinal cord injury in rats and its correlation with the p38MAPK/iNOS signaling pathway,” *Life Sciences*, vol. 92, no. 24–26, pp. 1215–1221, 2013.
- [109] O. Cevik, M. Ersahin, T. E. Sener et al., “Beneficial effects of quercetin on rat urinary bladder after spinal cord injury,” *The Journal of Surgical Research*, vol. 183, no. 2, pp. 695–703, 2013.
- [110] H. L. Song, X. Zhang, W. Z. Wang et al., “Neuroprotective mechanisms of rutin for spinal cord injury through anti-oxidation and anti-inflammation and inhibition of p38 mitogen activated protein kinase pathway,” *Neural Regeneration Research*, vol. 13, no. 1, pp. 128–134, 2018.
- [111] Z. Ma, Y. Lu, F. Yang et al., “Rosmarinic acid exerts a neuroprotective effect on spinal cord injury by suppressing oxidative stress and inflammation via modulating the Nrf2/HO-1 and TLR4/NF- κ B pathways,” *Toxicology and Applied Pharmacology*, vol. 397, p. 115014, 2020.
- [112] A. J. Shang, Y. Yang, H. Y. Wang et al., “Spinal cord injury effectively ameliorated by neuroprotective effects of rosmarinic acid,” *Nutritional Neuroscience*, vol. 20, no. 3, pp. 172–179, 2015.
- [113] X. Kong, S. Gong, L. Su, C. Li, and Y. Kong, “Neuroprotective effects of allicin on ischemia-reperfusion brain injury,” *Oncotarget*, vol. 8, no. 61, pp. 104492–104507, 2017.
- [114] R. Lv, N. Mao, J. Wu et al., “Neuroprotective effect of allicin in a rat model of acute spinal cord injury,” *Life Sciences*, vol. 143, pp. 114–123, 2015.
- [115] S. G. Liu, P. Y. Ren, G. Y. Wang, S. X. Yao, and X. J. He, “Alliin protects spinal cord neurons from glutamate-induced oxidative stress through regulating the heat shock protein 70/inducible nitric oxide synthase pathway,” *Food & Function*, vol. 6, no. 1, pp. 320–329, 2015.
- [116] Y. J. Zhang, X. Chen, L. Zhang et al., “Protective effects of 3,4-dihydroxyphenylethanol on spinal cord injury-induced oxidative stress and inflammation,” *Neuroreport*, vol. 30, no. 15, pp. 1016–1024, 2019.
- [117] P. Singer, A. R. Blaser, M. M. Berger et al., “ESPEN guideline on clinical nutrition in the intensive care unit,” *Clinical Nutrition*, vol. 38, no. 1, pp. 48–79, 2019.

- [118] R. Burgos, I. Breton, E. Cereda et al., “ESPEN guideline clinical nutrition in neurology,” *Clinical Nutrition*, vol. 37, no. 1, pp. 354–396, 2018.
- [119] C. Rowan and A. Kazemi, “An observational study of feeding practice in ventilated patients with spinal cord injury,” *Clin Nutr ESPEN*, vol. 37, pp. 107–113, 2020.
- [120] P. Aiello, S. Consalvi, G. Poce et al., “Dietary Flavonoids: Nano Delivery and Nanoparticles for Cancer Therapy,” *Seminars in Cancer Biology*, vol. 24, no. 19, pp. 30217–30222, 2019.
- [121] E. Toti, C. O. Chen, M. Palmery, D. Villaño Valencia, and I. Peluso, “Non-provitamin A and provitamin A carotenoids as immunomodulators: recommended dietary allowance, therapeutic index, or personalized nutrition?,” *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 4637861, 20 pages, 2018.
- [122] W. Chen, Z. Zhao, S. Zhao, L. Zhang, and Q. Song, “Resveratrol and puerarin loaded polymeric nanoparticles to enhance the chemotherapeutic efficacy in spinal cord injury,” *Biomedical Microdevices*, vol. 22, no. 4, p. 69, 2020.
- [123] I. Peluso, N. S. Yarla, R. Ambra, G. Pastore, and G. Perry, “MAPK signalling pathway in cancers: olive products as cancer preventive and therapeutic agents,” *Seminars in Cancer Biology*, vol. 56, pp. 185–195, 2019.
- [124] M. J. Brown, M. G. Ferruzzi, M. L. Nguyen et al., “Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressings as measured with electrochemical detection,” *The American Journal of Clinical Nutrition*, vol. 80, no. 2, pp. 396–403, 2004.
- [125] I. Peluso, L. Romanelli, and M. Palmery, “Interactions between prebiotics, probiotics, polyunsaturated fatty acids and polyphenols: diet or supplementation for metabolic syndrome prevention?,” *International Journal of Food Sciences and Nutrition*, vol. 65, no. 3, pp. 259–267, 2014.