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Review

Thymoquinone: An edible redox-active quinone for the pharmacotherapy of neurodegenerative conditions and glial brain tumors. A short review

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ABSTRACT

There exist few efficient agents in the neurological and neurosurgical armamentarium for treatment of neurotrauma, refractory seizures and high grade glial tumors. Pathophysiological conditions of diverse neural injuries have converging common pathways including oxidative stress and apoptosis. Targeted therapies have been throughly investigated, but limited success has been achieved until now. Phytochemical drugs may provide easily achievable and cheap adjunctive sources. Thymoquinone is an edible quinone obtained from *Nigella sativa* seed oil and exerts powerful antiinflammatory, antioxidant and antitumor activities in experimental models. Recently emerging studies conducted with animal models suggest that thymoquinone – bearing a very simple molecular structure – significantly crosses the blood brain barrier and exerts neuromodulatory activities. Indeed, in animal studies, the following actions of thymoquinone were demonstrated: 1—Protection against ischemic brain damage. 2—Reduction of epileptic seizures and associated cerebral oxidative injury. 3—Reduction of morphine tolerance and associated oxidative brain damage. 4—Anxiolytic effects and reduction of immobility stress-associated cerebral oxidative injury. 5—Reduction of diabetes-induced cerebral oxidative stress, 6—Reduction of cerebral oxidative injuries induced by noxious exposures including toluene, lead and ionizing radiation. Substantial *in vitro* data suggest that thymoquinone may be beneficial in treatment of glial tumors. However, there is no clinical study investigating its antitumor effects. In fact, thymoquinone suppresses growth and invasion, and induces apoptosis of glial tumor cells via degrading tubulins and inhibiting 20S proteasome, telomerase, autophagy, FAK and metalloproteinases. A simple and easily available agent may be a promising adjunctive treatment option in neurological and neurosurgical practice.

Contents

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1. Introduction

Human brain is particularly sensitive to oxidative and nitrosative injury due to several factors including abundance of polyunsaturated fatty acids, relatively low antioxidants, limited cell renewal capacity, high rates of oxidative metabolism and subsequent overproduction of reactive oxygen and nitrogen species [1]. In the central nervous system (CNS), oxidative and nitrosative stress results in acute and chronic neural injury. Pathophysiological mechanisms of diverse neural injuries including trauma, ischemia, epilepsy, and cerebral radiation necrosis have common pathways of oxidative stress and apoptosis. Phytochemical agents may bene beneficial in treatment of both degenerative and malignant diseases. Thymoquinone (Fig. 1), a natural drug with powerful antioxidant and antiinflammatory features would be one of these. High grade glial tumors constitute a major problem in neurooncological practice. Among them, glioblastoma is a grade IV glioma and remains the most lethal and the most common brain cancer in adults [2]. Despite advances in clinical management, median survival is approximately 15 months after initial diagnosis. Multiple factors lead to this poor outcome including tumor heterogeneity, a plethora of mutations, and highly infiltrative features of tumor cells [3]. Indeed, invasive brain tumor cells escape surgery and cause recurrence. Thymoquinone may interfere with several features of glioma pathogenesis, including proliferation, apoptosis and invasion.

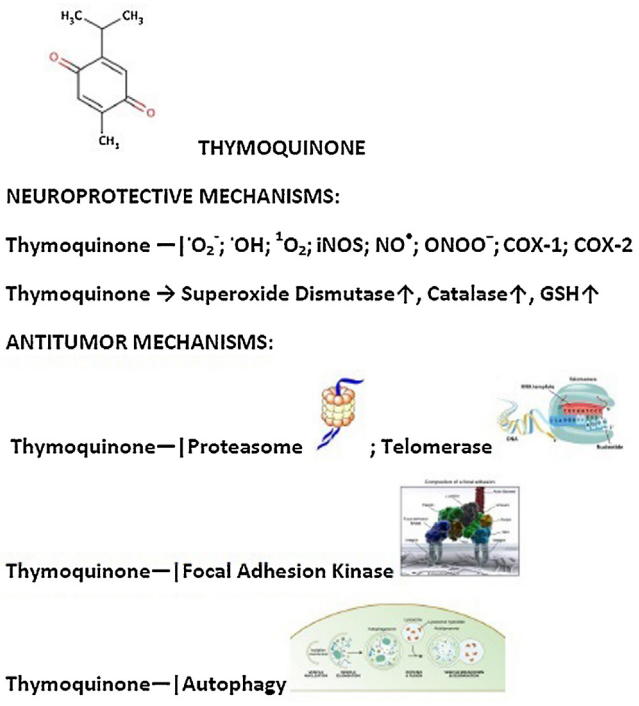

Fig. 1. Thymoquinone-Modified Molecular Pathways.

2. Description and chemicobiological interactions of thymoquinone, a major constituent of the *Nigella sativa* seed oil

Seed oil extracts of the black cumin (*Nigella sativa,* NS) have been used as a traditional medicine in the Middle East and India [4]. It was benefitted as a natural remedy for a number of diseases such as asthma, bronchitis, headache, eczema, diabetes and gastrointestinal disturbances [5]. *Nigella sativa* oil (NSO) also bears antipyretic, analgesic, anti-inflammatory, antimicrobial, and anticancer efficacies. Aqueous extract of *N. sativa* seeds inhibits production of nitric oxide (NO) by murine macrophages [5]. Seeds of the *Nigella sativa* contain a fixed oil (30% wt/wt) and a volatile oil (0.40–0.45%) [6]. Thymoquinone (2-methyl-5-isopropyl-1,4-benzoquinone) is the main constituent and the principal active ingredient of the volatile oil [4,6]. The volatile oil contains 18.4–24.0% thymoquinone [6]. Thymoquinone scavenges superoxide, hydroxyl and singlet oxygen radicals [7]. Thymoquinone also indirectly reduces reactive oxygen species (ROS) production. The inhibitory effect of thymoquinone against NO production (and thereby reduction of reactive nitric oxide species/RNS) includes inhibition of the iNOS (inducible nitric oxide synthase) protein synthesis in lipopolysaccharide-stimulated macrophages [7].

Thymoquinone protects organs against oxidative damage induced by a variety of free radical generating conditions and chemotherapy agents including doxorubicin cardiotoxicity, cisplatin nephropathy, ifosfamide Fanconi syndrome, and allergic encephalomyelitis [7]. Thymoquinone also exerts analgesic and anti-inflammatory actions and protects against chemical carcinogenesis. Anti-inflammatory and analgesic actions of NSO and thymoquinone may be related to inhibition of eicosanoid generation, namely thromboxane B2 and leucotrienes B4 (via inhibiting cyclooxygenase and 5-lipooxygenase, respectively), membrane lipid peroxidation and histamine release [5]. Thymoquinone acts as an inhibitor of both cyclooxygenase-1 and -2 [7].

Thymoquinone is of low toxicity (LD50 2.4 g/kg) and generally well tolerated when given subchronically up to 90 mg/kg/day for 90 days. In mice, its LD50 dose is 100–150 times higher than its effective antitumor dose when administrated orally. Both NSO and thymoquinone have also antimutagenic efficacy and reduce toxicity induced by standard anticancer agents. Thymoquinone is a substrate for quinone reductase that forms dihydro-thymoquinone [7]. Thymoquinone induces hepatic quinone reductase activity. It was hypothesized that upregulation of quinone reductase in hippocampal pyramidal cell neurons is a neuroprotective response to dihydrothymoquinone, based on the similarity between dihydrothymoquinone and *tert*-butyl-hydroquinone.

3. Neuroprotective effects of thymoquinone shown in *in vivo* studies

3.1. Thymoquinone protects against ischemic brain damage

Ischemic cerebral injury is a major cause of adult disability. Transient global cerebral ischemia (forebrain ischemia) due to