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Elucidating the Role of Protandim and 6-Gingerol in Protection Against Osteoarthritis (OA)

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Protandim and 6-gingerol, two potent nutraceuticals, have been shown to decrease free radicals production through enhancing endogenous antioxidant enzymes. In this study, we evaluated the effects of these products on the expression of different factors involved in osteoarthritis (OA) process. Human OA chondrocytes were treated with 1 ng/ml IL-1β in the presence or absence of **Protandim** (0–10 μg/ml) or 6-gingerol (0–10 μM). OA was induced surgically in mice by destabilization of the medial meniscus (DMM). The animals were treated weekly with an intraarticular injection of 10 μl of vehicle or **Protandim** (10 μg/ml) for 8 weeks. Sham-operated mice served as controls. In vitro, we demonstrated that **Protandim** and 6-gingerol preserve cell viability and mitochondrial metabolism and prevented 4-hydroxynonenal (HNE)□induced cell mortality. They activated Nrf2 transcription factor, abolished IL-1β-induced NO, PGE_2, MMP-13, and HNE production as well as IL-β-induced GSTA4-4 down-regulation. Nrf2 overexpression reduced IL-1β-induced HNE and MMP-13 as well as IL-1β-induced GSTA4-4 down-regulation. Nrf2 knockdown following siRNA transfection abolished **Protandim** protection against oxidative stress and catabolism. The activation of MAPK and NF-κB by IL-1β was not affected by 6-gingerol. In vivo, we observed that Nrf2 and GSTA4-4 expression was significantly lower in OA cartilage from humans and mice compared to normal controls. Interestingly, **Protandim** administration reduced OA score in DMM mice. Altogether, our data indicate that Protandim and 6-gingerol are essential in preserving cartilage and abolishing a number of factors known to be involved in Osteoarthritis (OA) pathogenesis.