PERSPECTIVE

Translational perspective: is cinnamon a suitable agent for cognitive impairment and Alzheimer's disease associated with brain trauma?

Cinnamon, is an exotic spice and a major constituent of our food which is commonly used in different areas of the world for the treatment of various diseases (Kawatra et al., 2015). Besides its anti-inflammatory, anti-diabetic and anti-cancer properties, cinnamon also exerts strong brain protective and pro-cognitive effects in various models of neurodegeneration (Kawatra et al., 2015; Kelestemur et al., 2016) (**Figure 1**). Traumatic brain injury (TBI) is characterized with significant vascular, neuronal and axonal damage that is associated with critical oxidative injury and neuroinflammation (Kelestemur et al., 2016). Clinical studies have already conferred that pre and post-injury systemic inflammation could modify the subsequent prognosis of brain injury (Yulug et al., 2018). Moreover, many pharmacological agents were failed to show a clinical neuroprotective effect after TBI suggesting that there is an emergency need for novel brain protective therapeutic strategies to improve the clinical outcomes. However, although there are increasing promising experimental data, many clinical trials were failed to change the clinical endpoint after TBI (Kelestemur et al., 2016; Yulug et al., 2018). Additionally, studies have already indicated that drug-drug interactions play an essential role in the development of pharmacotoxic side effects (Yulug et al., 2018). Taken together, these findings might further indicate that a single agent which is acting on multiple cell death pathways may exert a higher neuroprotective activity. Here, cinnamon might be a novel clinical candidate agent for TBI with its multifaceted neuroprotective and procognitive effects, and its superior safety profile. Interestingly, it has been recently revealed that brain trauma has been not only associated with cognitive impairment but also increase the risk of the development of Alzheimer's disease (Cristoforti and Levin, 2015; Kawatra et al., 2015; Kelestemur et al., 2016; Yulug et al., 2018).

TBI and cognition: TBI is affecting more than 10 million people worldwide leading to critical alteration in brain pathophysiology. TBI pathophysiology includes blood-brain barrier breakdown, diffuse axonal damage, and subsequent edema and neuronal cell death (Cristoforti and Levin, 2015; Kawatra et al., 2015; Kelestemur et al., 2016; Yulug et al., 2018). Despite these, the clinical presentation of TBI is likely underestimated since many patients with mild TBI do not seek medical attention due to their latent cognitive symptoms (*i.e.*, memory, information processing speed, attention and executive function) (Cristoforti and Levin, 2015). Studies have already indicated that deterioration of cognitive and social functioning after TBI depend on the lesion extent, location, and recovery neuroplasticity mechanisms although there is still no evidence of neuroimaging abnormality (Cristoforti and Levin, 2015; Kawatra et al., 2015; Kelestemur et al., 2016; Yulug et al., 2018). These findings together, suggested that there is a need for advanced neuroimaging techniques (*i.e.*, functional blood oxygen level-dependent MRI, positron emission tomography that might enlighten us on subtle pathophysiological correlates of cognitive dysfunction after mild-TBI. An example of this is the study carried out by Martucci et al. (2018) suggesting that optic coherence tomography could be a suitable neuroimaging approach in determining the effect of iatrogenic brain damage on retinal ganglion cell death which is mediated by transsynaptic retrograde degeneration.

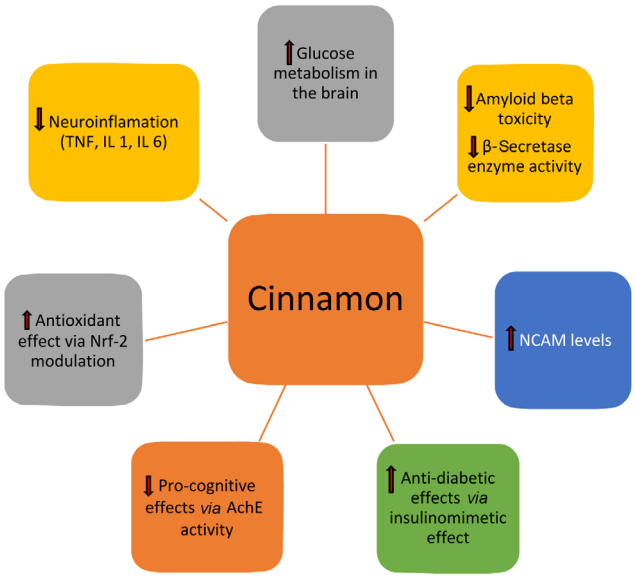

Figure 1 Cinnamon effects in various models of neurodegeneration.
TNF: Tumor necrosis factor; IL: interleukin; AchE: acetylcholinesterase; NCAM: neural cell adhesion molecule; Nrf-2: nuclear factor-erythroid 2 related factor 2.

TBI and Alzheimer's disease: Even a mild TBI can have serious and lasting effects, such as, dementia which is the most fearest long-term complication of the brain trauma (Shively et al., 2012). Agreeably, a number of epidemiologic studies indicate that TBI in early to midlife is associated with significantly increased risk of dementia in late life, which appears to be much higher in patients with multiple TBIs (Shively et al., 2012). In line with this, many experimental models and clinical data have revealed that TBI results in neurodegeneration that continues at least 1 year after injury (Bramlett and Dietrich, 2002). Although the exact pathophysiological mechanism is unclear recent experimental and clinical studies suggested that several proteins associated with neurodegenerative disease in humans accumulate following experimental TBI in rodents (Bramlett and Dietrich, 2002; Shively et al., 2012). These include the release of various excitatory amino acids (*i.,e*, glutamate, aspartate), free oxygen radicals and other potentially critical factors such as the endogenous opioids, catecholamines, nitric oxide and inflammatory factors such as tumour necrosis factor and interleukins which have been already shown to be associated with amyloid accumulation (Bramlett and Dietrich, 2002; Chen et al., 2004; Shively et al., 2012). Diffuse axonal injury including the dysfunction of the axonal cytoskeleton and axoplasmic membrane transport is another factor contributing to the neuropathological consequence of brain trauma (Bramlett and Dietrich, 2002; Chen et al., 2004). Interestingly, recent studies have also conferred that amyloid precursor protein, beta-amyloid peptide, beta-secretase, presenilin-1 and caspase 3 are up-regulated after brain trauma (Bramlett and Dietrich, 2002; Chen et al., 2004). Accordingly, accumulated intra-axonal amyloid, Beta-amyloid peptide and hyperphosphorylated tau has been recently defined in transgenic mice models after TBI (Bramlett and Dietrich, 2002; Chen et al., 2004; Shively et al., 2012). Taken together, these findings have led to the hypothesis that therapeutic implications such as anti-inflammatory, anti-amyloid and pro-cognitive therapies may have a multifaceted role in the management of TBI related cognitive dysfunction and Alzheimers disease.

Cinnamon after TBI: Studies investigating the therapeutic efficacy of cinnamon in inflammatory neurodegenerative disorders have revealed that compounds endogenous to cinnamon exerted significant anti-Alzheimer effect through improved insulin signalling and cognitive dysfunction (Kawatra et al., 2015). In line with this, experimental models of Alzheimer's disease and diabetes mellitus have suggested that cinnamon showed significant pro-cognitive effects that contained decreased oxidative stress and declined streptozotocin-induced impairment in acetyl cholinesterase activity (Bramlett and Dietrich, 2002; Chen et al., 2004; Shively et al., 2012;

Jain et al., 2014). The anti-amyloid activity of cinnamon was confirmed with further studies showing that cinnamon significantly suppressed the β-secretase enzyme activity (Bramlett and Dietrich, 2002; Chen et al., 2004; Shively et al., 2012; Jain et al., 2014). Recent data also revealed that cinnamon regulated glucose levels and exerted insulinomimetic effects *via* signaling proteins, peroxisome proliferator activated receptor and the expression of insulin-sensitive glucose transporters (Sheng et al., 2008). Considering the fact that even mild-increased glucose levels are an important risk for Alzheimer's disease (Kawatra et al., 2015), it is logical to think cinnamon might have a multifaceted therapeutic role in Alzheimer's disease.

In our very recent study, we have evaluated cinnamon's neuroprotective activity after TBI in mice (Yulug et al., 2018). Thirty minutes after performing the cryogenic brain trauma model, we have applied 10 mg/kg intraperitoneally cinnamon and analyzed the infarct and edema volumes along with the expression of inflammatory and anti-oxidant protein levels. Not surprisingly, we have shown for the first time that cinnamon reduced the infarct volume, edema formation and supressed inflammation and oxidative injury after TBI which suggested that cinnamon could be a promising therapeutic agent for neurodegenerative disorders characterized by increased inflammation and oxidative stress. Another important message of our study was that promising neuroprotective agents should be applied within the latent time period where increased oxidative injury and inflammation are deemed to play a vital role in the pathogenesis of TBI. Considering that multi-drug interactions may also limit the neuroprotective activity of each single candidate agent, it is not unreasonable to assume that a multi-potent single agent acting on multiple pathophysiological cascades might provide a greater neuroprotective effect. However, many clinical trials have failed to show an effective neuropharmacological treatment for the primary and secondary outcomes after TBI in humans (*i.e.*, clinical and cognitive outcomes). In our previous experimental TBI study (Yulug et al., 2018), we were not surprised to reveal that cinnamon treatment regulated various anti-oxidant enzymes and inflammatory cytokines. However, the most interesting finding was that cinnamon significantly increased nuclear erythroid factor-2 which is a potent inductor of the endogenous anti-oxidant pathways and regulates the inflammatory and anti-oxidative pathways through nuclear factor kappa B during the TBI (Kelestimur et al., 2016; Yulug et al., 2018). It should be noted that we also have revealed increased neural cell adhesion molecule levels after cinnamon treatment that is an important mediator of neurogenesis and axonal growth (Murray et al., 2016; Yulug et al., 2018). From a clinical perspective, a recent human study has revealed that polysialated neural cell adhesion molecule levels were significantly reduced in the entorhinal cortex that were inversely correlated with hyperphosphorylated tau load (Murray et al., 2016). In paralell with that, amyloid-β-dependent disruption of hippocampal neural cell adhesion molecule 2 augmented significantly the synapse loss in Alzheimer's disease (Leshchyns'ka et al., 2015). In line with this, a recent human study has revealed that reduced polysialated neural cell adhesion molecule levels were inversely correlated with hyperphosphorylated tau load in the entorhinal cortex (Murray et al., 2016).

Conclusion: Cinnamon exerts not only neuroprotective activity through suppressing the inflammation and oxidative injury in TBI but also might have a therapeutic role in TBI-related dementia with its well-known cognitive enhancer and anti-amyloid effects. These above-mentioned effects of cinnamon could be valuable regarding the rapidly increasing interest in the use of cinnamon in these particular groups of patients. From a translational perspective, cinnamon could be also an essential part of the preventive nutritional strategy in chronic neurodegenerative diseases. For instance, because cinnamon is a non-toxic and also an economical natural compound, a cinnamon high rich diet could play a critical role in the prevention of slowly progressing metabolic and neurological disorders.

In future investigations, it might be possible to evaluate the neuroprotective and pro-cognitive effect of cinnamon and their correlates with cognitive scores after TBI and TBI related dementia. Achieving clinically relevant data in such well-designed experimental studies may tailor our treatment to cognitively impaired trauma patients. Moreover, well-designed randomised clinical research including the combination of prospective functional neuroimaging data (*etc.* amyloid-positron emission tomography) and clinical assessment scores would help us to understand the clinical relevance of the neuroprotective and pro-cognitive effect of cinnamon after TBI. This also may offer a significantly cost-effective alternative to the expensive anti-dementia neuropharmacologic treatments, especially in developing world countries.

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References

Bramlett HM, Dietrich DW (2002) Quantitative structural changes in white and gray matter 1 year following traumatic brain injury in rats. Acta Neuropathol 103:607-614.

Chen XH, Siman R, Iwata A, Meaney DF, Trojanowski JQ, Smith DH (2014) Long-term accumulation of amyloid-beta, beta-secretase, presenilin-1, and caspase-3 in damaged axons following brain trauma. Am J Pathol 165:357-371.

Cristofori I, Levin HS (2015) Traumatic brain injury and cognition. Handb Clin Neurol 128:579-611.

Jain S, Sangma T, Shukla SK, Mediratta PK (2015) Effect of Cinnamomum zeylanicum extract on scopolamine-induced cognitive impairment and oxidative stress in rats. Nutr Neurosci 18:210-216

Kawatra P, Rajagopalan R (2015) Cinnamon: Mystic powers of a minute ingredient. Pharmacognosy Res 7:1-6.

Kelestemur T, Yulug B, Caglayan AB, Beker MC, Kilic U, Caglayan B, Yalcin E, Gundogdu RZ, Kilic E (2016) Targeting different pathophysiological events after traumatic brain injury in mice: Role of melatonin and memantine. Neurosci Lett 612:92-97.

Leshchyns'ka I, Liew HT, Shepherd C, Halliday GM, Stevens CH, Ke YD, Ittner LM, Sytnyk V (2015) Aβ-dependent reduction of NCAM2-mediated synaptic adhesion contributes to synapse loss in Alzheimer's disease. Nat Commun 6:8836

Martucci A, Cesareo M, Nucci C, Mancino R (2018) Macular ganglion cells alteration in a patient with left homonymous hemianopia subsequent to surgical excision of an arteriovenous malformation. Am J Ophthalmol Case Rep 12:9-14.

Murray HC, Low VF, Swanson ME, Dieriks BV, Turner C, Faull RL, Curtis MA (2016) Distribution of PSA-NCAM in normal, Alzheimer's and Parkinson's disease human brain. Neuroscience 330:359-375.

Sheng X, Zhang Y, Gong Z, Huang C, Zang YQ (2008) Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors. PPAR Res 2008:581348.

Shively S, Scher AI, Perl DP, Diaz-Arrastia R (2012) Dementia resulting from traumatic brain injury: what is the pathology? Arch Neurol 69:1245-1251.

Yulug B, Kilic E, Altunay S, Ersavas C, Orhan C, Dalay A, Tuzcu M, Sahin N, Juturu V, Sahin K (2018) Cinnamon polyphenol extract exerts neuroprotective activity in traumatic brain injury in male mice. CNS Neurol Disord Drug Targets 17:439-447.

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