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# Preventing and Reversing "Microglia-Aging" by Nature Materials for Slow Brain-Aging

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## Abstract

Mitochondrial DNA (mtDNA), which encodes components of the mitochondria electron transfer complexes, is highly susceptible to damage produced by reactive oxygen species (ROS), due to its close proximity to ROS generated through the respiratory chain and the paucity of protective histones. Accumulation of mtDNA damages during aging result in the reduced expression of the mitochondria electron transfer complexes, especially complex I. The resultant reduced activity of complex I further increases the generation of ROS, forming a vicious cycle. During aging, the accumulation of oxidative mtDNA damages is prominently found in the brain resident microglia. Increased intracellular ROS, in turn, drives microglia to provoke excessive neuroinflammation in the aged brain through activation of nuclear factor-κB (NF-κB). Hypoxia activates microglia to induce the generation of mitochondria-derived ROS and the subsequent activation of NF-κB signaling pathway to produce pro-inflammatory mediators, which impairs the cognitive functions. Propolis, a resinous substance produced by honeybees, significantly inhibits the hypoxia-induced neuroinflammatory responses by microglia. Furthermore, propolis and *Ratanasampil*, a traditional Tibetan medicine, improve the cognitive functions of the people who are living at high altitude. Considering that the daily exposure to hypoxia is one of risk factors for the aging-related cognitive impairments, these pharmacological approaches that prevent and reverse "microglia-aging" may become a most promising future research avenue for preventing the aging-related cognitive impairments.

**Keywords:** Cognitive impairments; Microglia; Oxidative mitochondrial DNA damage; Nature materials; Neuroinflammation

**Abbreviations:** AD: Alzheimer's Diseases; IL-1β: Interleukin-1β; Aβ: amyloid-κ; LTP: long-Term Potentiation; NF-κB: Nuclear Factor-κB; RNSP: Ratanasampil; ROS: Reactive Oxygen Species; TNF-α: Tumor Necrosis Factor-α; TGF-β1: Transforming Growth Factor-β1

## Introduction

By the year 2030, roughly 20% of the population will be over 65 years of age in the world [1]. As the mean life expectancy continues to increase, it is an urgent issue to understand aging accelerators that are responsible for cognitive impairments associated with normal aging and Alzheimer's disease (AD). Better understanding of aging accelerators will help to invent the strategies for preventing the age-related cognitive impairments. Microglia, the resident mononuclear phagocyte population in the brain, are activated either chronically or pathologically to influence the neuronal environment. We have provided evidence that the excessive reactive oxygen species (ROS) and pro-inflammatory mediators produced by microglia cause neuroinflammation during aging [2]. On the other hand, hypoxia can drive microglia to generate ROS [3-7], resulting in NF-κB-dependent excessive production of pro-inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [8-12]. Furthermore, microglia-mediated neuroinflammation is closely associated with AD pathogenesis [13], because overproduction of pro-inflammatory mediators by microglia triggers neuroinflammatory responses to promote neuronal damages and deposition of amyloid-β (Aβ) [14,15]. On the other hand, anti-inflammatory agents improve cognitive functions in AD [16,17]. Recently, we have found that propolis, a resinous substance produced by honeybees as a defense against intruders, inhibits the hypoxia-induced production of pro-inflammatory mediators by microglia through inhibiting the generation of mitochondria-derived ROS and the subsequent activation of NF-κB signaling pathway [12]. Furthermore, propolis improves the cognitive functions of the people living at the high altitude [18]. On the other hand, *Ratanasampil* (RNSP), a traditional Tibetan medicine composing 70 nature herbal materials, improves the cognitive functions in mild-to-moderate AD patients living at high altitude through reducing the levels of pro-inflammatory mediators and deposition of Aβ [18]. In this review, we will highlight and discuss our proposed concept of "microglia-aging", which refers to the concept that microglia are the most potent aging accelerators in the brain, in cognitive impairments associated with normal aging and AD. We will also provide a scope that nature materials could provide significant benefits in elderly people with mild-to-moderate cognitive impairments.

## Microglia as Potent Aging Accelerators of The Brain: "Microglia-Aging" Concept

There is considerable variability among individuals in the extent of decline in the cognitive functions [19]. It is noted that the cognitive functions in elderly people are severely impaired during infection [20], surgery [21] or psychological stress [22], thus indicating that brain is sensitive to systemic challenges during aging [19,23-25]. Microglia, the

resident mononuclear phagocytes in the brain, is activated chronically to influence the neuronal environment during aging [2]. Perry et al. [26] first provided the concept of "primed microglia" [26-28]. Primed microglia is characterized by shortened processes and the increased expression of cell surface antigens similar to activated microglia, but they are devoid of the ability to secrete pro-inflammatory molecules. Systemic inflammatory signals activate primed microglia to provoke exaggerated neuroinflammation in comparison to normally activated non-primed microglia. The basal levels of pro-inflammatory mediators are increased during aging, leading to enhanced lipopolysaccharide (LPS)-induced sickness behavior in the aged animals. These observations suggest that microglia in the aged brain are primed and over-reacted to systemic challenges [29-33]. More recently, the mean level of IL-1β secreted by primary cultured microglia prepared from the aged brains is significantly higher than that from the young brains [12,29,34]. These observations further support our proposed concept of "microglia-aging" [2,35] (Figure 1).

The complex learning paradigms have revealed that the brain is changed structurally and functionally even in healthy middle-aged individuals (over 50 years in human) [36]. The prefrontal white matter volume is significantly decreased even in the middle-age [37]. Furthermore, using adjuvant arthritic rats, an animal model of stable chronic systemic inflammatory disease, we have found that microglia induce an age-dependent differential responses to chronic systemic inflammatory challenges [38-40]. In the young adult rats, microglia produces anti-inflammatory mediators, including IL-10 and TGF-β1, during chronic systemic inflammation. In contrast, microglia produces excessive IL-1β, but less IL-10 and TGF-β1 in the middle-aged rats [41-43]. These observations strongly suggest that microglia can be primed even in the middle-age and over-react to chronic systemic inflammation. Furthermore, oxidative mitochondrial DNA (mtDNA) damages are prominently found in microglia, suggesting that over production of ROS can be a cellular mechanism for priming of microglia after systemic inflammatory challenges [2,29]. The primed microglia cannot be reversed to a ground state of quiescent central housekeeping function, thus suggesting that "microglia-aging" is associated with disappearance of their abilities for maintaining homeostasis in microenvironment of the brain [2].

## Acceleration of "Microglia-Aging" during Hypoxia

Brain is highly susceptible to being damaged by hypoxia because of its high demand for oxygen supply [44]. Function as the resident innate immune cells in the brain, microglia constitute the first line of defense against brain insults [45,46]. Hypoxia is generally accepted as the neuroinflammatogens in the brain, because hypoxia activates microglia to provoke excessive secretion of pro-inflammatory mediators, including IL-1β, TNF-α and IL-6 [7-9,12]. We have previous found that excessive production of ROS due to the increased oxidative mtDNA damages in microglia is responsible for exaggerated neuroinflammatory responses in the aged animals after treatment with LPS, because the increased intracellular ROS level activates NF-κB signaling pathway which regulates the expression of several pro-inflammatory mediators [2]. Hypoxia can drive microglia to generate ROS [3-6], and we have recently found that hypoxia activates NF-κB signaling pathway to induce exaggerated inflammatory responses by microglia [12] (Figure 1).

The brain is highly vulnerable to hypoxic stress due to its high oxygen requirement and therefore, low oxygen availability at high altitudes results in cognitive impairments [47]. High altitude-induced cognitive impairments draw a special concern because this problem compromises mental performance [48,49]. We have previously reported that higher number of elderly people living at high altitude suffers from declines in memory and cognitive functions in comparison to that of elderly people living at the ground level [50]. A similar decline in memory arising from hypoxic exposure has been also reported in experimental animals [51]. More recent observation shows that high altitude-exposure deteriorates mainly attention, perception, judgment and working memory [52].
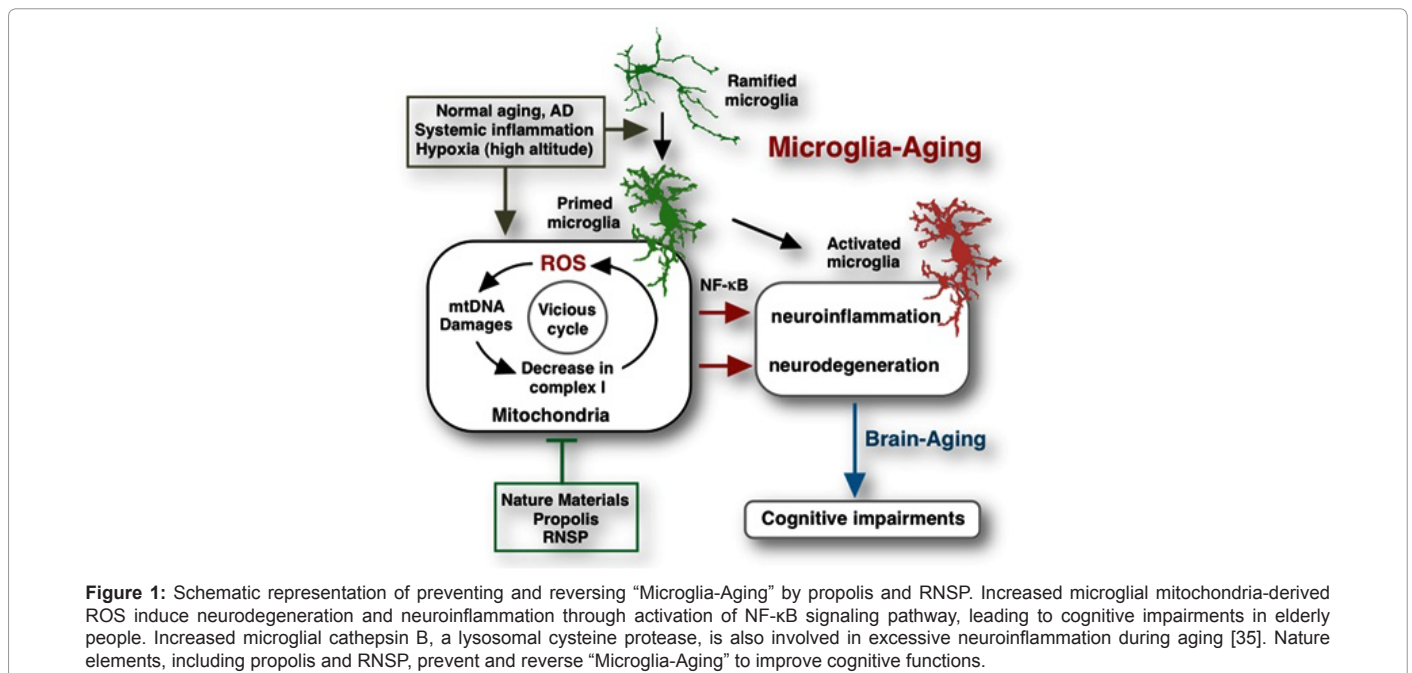
Stroke is the most common form of hypoxia-ischemic brain injury. In the western world, over 70% of individuals experiencing a stroke is over 65 years of age. Since life expectancy continues to grow, the absolute number of individuals with stroke will further increase in the future [53]. Activation of NF-κB pathway is involved in hypoxia-ischemic brain injury [53-55], and microglia are clarified as the major cell population leading to NF-κB-dependent up-regulation of pro-inflammatory mediators, including IL-1β and TNF-α during stroke [56,57].

The chronic hypoxia contributes to the onset and progression of AD [12,58,59], because hypoxia activates microglia to produce pro-inflammatory mediators, including IL-1β TNF-α and IL-6 [7-9,12]. Microglia-mediated neuroinflammatory responses are closely associated with AD pathogenesis [13], because pro-inflammatory responses mediated by microglia promote neuronal cell damage and excessive Aβ deposition [13,60]. It is also known that microglia-mediated neuroinflammatory responses promote cognitive deficits in AD patients [61,62]. Taken together, hypoxia activates NF-κB signaling pathway to accelerate cognitive impairments through promoting "microglia-aging".

It is well known the close link between hippocampal functions and cognitive functions [63]. Therefore, we will discuss how "microglia-aging" impact on cognitive functions. Hippocampal long-term potentiation (LTP) is widely accepted as a cellular basis of learning and memory [64]. The exceeded expression levels of pro-inflammatory mediators in the hippocampus are associated with impairment of LTP [65-67]. In particularly, IL-1β potently impairs the formation of the CA1 region [68] and the dentate gyrus of the hippocampus [69,70]. Recently, we have found that the hippocampal LTP is significantly impaired in the middle-aged, but not young adult, rats during chronic systemic inflammation [71].

## Preventing and Reversing "Microglia-Aging" by Nature Materials

There is increasing evidence that nature materials can provide significant benefits in dementia by their traditional usages [72]. Propolis has relevant therapeutic properties that have been used since ancient times. The chemical composition of propolis depends on the local floral at the site of collection [73-75]. In addition to the fact that propolis has anti-oxidative and anti-inflammatory effects [76-78], we recently provided the first evidence that propolis can significantly inhibit the secretion of IL-1β, TNF-α and IL-6 by microglia through inhibition of the activation of NF-κB signaling pathway [12]. Furthermore, propolis significantly inhibits oxidative mtDNA damages, which are responsible for the induction of excessive ROS and the subsequent activation of NF-κB signaling pathway. Moreover, propolis significantly inhibits the increased expression of 8-oxo-deoxyguanosine, a biomarker for oxidative DNA damages [79], which was observed mainly in the mitochondria of cortical microglia after hypoxia. On the other hand, effects of RNSP on the oxidative mtDNA damages are to be elucidated in future studies. With the line of our previous observations that

**Figure 1:** Schematic representation of preventing and reversing "Microglia-Aging" by propolis and RNSP. Increased microglial mitochondria-derived ROS induce neurodegeneration and neuroinflammation through activation of NF-κB signaling pathway, leading to cognitive impairments in elderly people. Increased microglial cathepsin B, a lysosomal cysteine protease, is also involved in excessive neuroinflammation during aging [35]. Nature elements, including propolis and RNSP, prevent and reverse "Microglia-Aging" to improve cognitive functions.

oxidative mtDNA damages, in turn, impair the respiratory chain, forming a vicious cycle to promote the ROS generation [2], propolis may prevent and reverse "microglia-aging" through its anti-oxidant property [76-80] (Figure 1).

People living in Qinghai-Tibet Plateau experience chronic hypoxia at high altitude. Current medical researches on the age-related cognitive impairment spay a special attention on this area, because higher number of the elderly population suffers from declines in memory and cognitive functions [81,82]. RNSP, one of the most important Tibetan medicines, is composed of 70 nature herbal materials [83]. RNSP is used to treat cerebrovascular diseases such as cerebral hemorrhage, cerebral infarction, epilepsy and brain concussion. Recently, clinical studies have revealed that RNSP has sedative and anti-convulsant effects, improves memory and circulation, and reduces platelet aggregation and antithrombotic properties [84,85]. Our previous studies have also showed that RNSP improves learning and memory in a mouse model of AD (Tg2576) [86,87] and improves cognitive functions in mild-to-moderate AD patients living at high altitude [18]. Furthermore, our preliminary clinical studies for people living at high altitude show that the propolis-treated elderly group obtained significantly higher scores of cognitive tests than the non-treated elderly group [18]. Moreover, both RNSP and propolis reduce the mean level of pro-inflammatory mediators, including IL-1β, TNF-α and IL-6 in the activated macrophages as well as in serum of peripheral blood of human, indicating that they also ameliorate systemic inflammatory challenges [18,88]. As we have discussed above, microglia can be primed even in the middle-age to sensitize to systemic inflammatory challenges. Therefore, the pharmacological approaches using nature materials that prevent and reverse "microglia-aging" may become a most promising future research avenue for improving cognitive functions of elderly people (Figure 1).

## Conclusion

We provide the scope that "microglia-aging" works as a brain-aging accelerator, which is associated with cognitive impairments during normal aging and AD. Propolis and RNSP, nature materials, can improve cognitive functions of elderly people through preventing and reversing "microglia-aging" (Figure 1).

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