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The neuroprotective attribution of *Ocimum basilicum*: a review on the prevention and management of neurodegenerative disorders

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Abstract

Background: Bioactive principles from various natural resources including medicinal herbs have always played a crucial role in healthcare settings and increasingly became key players in drug discovery and development for many biopharmaceutical applications. Additionally, natural products (NPs) have immense arrangement of distinctive chemical structures with diverse functional groups that motivated numerous investigators including synthetic chemists to discover new therapeutic entities. Numerous pre-clinical investigations involving the animal models have evident the usefulness of these NPs against various human diseases including neurodegenerative disorders (NDs).

Main text: *Ocimum basilicum* Linn (*O. basilicum* L.), also known as sweet basil, is well practiced in traditional healthcare systems and has been used to treat various human illnesses, which include malaria, skin disease, diarrhea, bronchitis, dysentery, arthritis, eye diseases, and insect bites and emphasize the significance of the ethno-botanical approach as a potential source of novel drug leads With the growing interest in advanced techniques, herbal medicine and medicinal plants explorations are still considered to be a novel resource for new pharmacotherapeutic discovery and development. *O. basilicum* L and its bioactive principles including apigenin, eugenol, myretenal, β-sitosterol, luteolin, rosmarinic acid, carnosic acid, essential oil (EO)-rich phenolic compounds, and others like anthocyanins and flavones could be of therapeutic values in NDs by exhibiting their neuro-protective efficacy on various signaling pathways. The present comprehensive review collected various related information using the following searching engines such as PubMed, Science Direct, Google Scholar, etc. and focused mainly the English written documents. The search period comprised of last two decades until present.

Conclusion: Although these efficacious plant genera of prime importance and has potential medical and socioeconomic importance, yet the pivotal evidence for its neuroprotective potential in novel clinical trials remains lacking. However, with the available wealth of obtainable literature on this medicinal plant, which supports this review and concludes that *O. basilicum* L may function as a promising therapeutics for the treatment of NDs.

Keywords: *Ocimum basilicum*, Neuro-protection, Prevention, Phytoconstituents, Neurodegeneration, NPs

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Background

Neuronal atrophy often described as neurodegeneration caused by degradation and subsequent loss of functional neurons which is predominantly witnessed among elderly population as wide spectrum chronic neurodegenerative diseases (NDs) of the central nervous system (CNS) [1–3]. The deficiency of quality treatment results to enormous socio-economic burdens [4]. Normally, NDs are described as characteristic loss of loss of neurons and their functions in numerous regions of the CNS, which include Parkinson's disease (PD), in which loss of dopaminergic nigrostriatal neurons are characteristic features, whereas in Huntington's disease (HD), a loss of medium-sized striatal spiny neurons and diffuse cerebral atrophy was evident in Alzheimer's disease (AD). Besides the above, primary dystonia or essential tremor and a few other motor defects/impairments are also denoted as NDs [5, 6].

Over the years, NDs share few clinical characteristics like the relentless progression of the disease even for decades [7]. Beyond the known well-characterized pathogenic causative mechanisms of individual illnesses, neurodegeneration is considered as the gradual loss of functional properties of neurons by the various chains of events leading to cell death, which represents the key point of this group of diseases [8]. Although numerous immense strive have been made to recognize the pathophysiology of NDs and their related technological advancements to address the issues pertaining to NDs, but little only achieved in developing effective therapies [9]. Moreover, the current therapies are adequate to alleviate symptoms only, not to stop the progress of the disease.

Contributing factors for the formation of neurodegeneration

Though pathophysiology of NDs along with the available treatment interventions for NDs, it is still necessary to brief the causative factors like hereditary, environmental, and oxidative stress and various other factors, etc., which are involved in the formation of NDs, which will shine more light on the investigators, who are involved in the discovery of new therapeutic options.

Role of genetics and hereditary

In the past few decades, various discoveries made our understanding of the etiology, causative genes, and mechanisms involved in the formation of hereditary NDs and promoted to identify the development of newer therapies. For example, in ADs, there are penetrant mutations in three genes like amyloid protein precursor (APP), PSEN 1, and PSEN 2, which are accountable for the onset of early familial AD. Studies have identified 8-causative genes (e.g., UCH-L1, a-synuclein, PINK1, parkin, DJ-1, OMI/HTRA2, LRRK2, and ATP13A2) and 4 additional loci of linkage across the genome (PARK3, 10, 11, 12) responsible for PD; however, still pending characterization and/or replication exists [10, 11].

Role of oxidative stress

It is well established that oxidative stress is the major cause of neural atrophy; however, its associated consequence remains elusive. However, in general, neuronal degradation caused by mitochondrial damage and oxidative stress results in DNA damage [12]. Mitochondrial and endoplasmic reticulum enzymes like P450 are some of the endogenous sources of reactive oxygen species (ROS) [13] together with oxidative radicals from cellular catabolism are responsible for the development of aging related degenerative disorders [14]. The natural antioxidant defence system exists in the human body comprised of glutathione, catalase, and superoxide dismutase (SOD) neutralizes these radical oxidants [15–17]. Besides, the continued accumulation of radical species in an impaired oxidant defence environment initiates neuronal cell death together with the involvement of pro-apoptotic Bcl-2 family members [18]. Human brains are highly susceptible to oxidative strains [19]. The brain has a high oxygen demand and contains high levels of polyunsaturated FAs mostly in the cell membranes act as substrates in the lipid peroxidation process [20]. The huge presence of oxidized polyunsaturated fatty acids (PUFAs) like arachidonic linoleic acid [19, 21] mostly worsens NDs symptoms [22].

Role of environmental factors

Besides, various environmental factors also contribute to the progression of NDs. Prolonged exposure of manganese and few toxic solvents are associated with mitochondrial dysfunction and accumulation of α-synuclein in PD [23]. In line with this, mercury and Lead increase the accumulation of tau protein and Aβ plaques, both of these involved in the formation of AD. Though these metal elements are essential for many biological reactions, interruption in their homeostasis results in free radical production. Normally, intracellular iron is bound by ferritin as an insoluble ferrihydrite form. 6-hydroxydopamine (6-OHDA), a well-known neurotoxin reduces core iron to liberate ferrous form. The reduced ferrous form stimulates lipid peroxidation; however, this process inhibited by an iron chelator deferoxamine. Studies have shown occupational exposure to pesticides cause neuronal impairment in aged people, thereby highlighting the toxic role of pesticides [24]; however, the consumption of sufficient amount of fruits, vegetables, and fish oil rich in omega-3 reduce the risk of dementia and AD with the involvement of apolipoprotein E (APOE-ε4) [25].

Role of protein misfolding and aggregation

Proteins are complex biomolecules, which are essential for various fundamental cellular processes. Long stretched amino acid chains and polypeptide chains folded as 3D structures to attain its functional state [26], which is required for the normal functional of the specific protein [27]. The truncated or misfolded proteins may lead to clumps or aggregation formation mainly in the hydrophobic regions [28]. Since AD and PD are classical example of protein-misfolding of NDs are caused by the accumulation of abnormal misfolded proteins, subsequent deposition of the aggregated plaques, and associated with various cellular dysfunctions [29], which are normally protected by molecular chaperons [30]. Firstly, the protein chaperons bind with unfolded proteins and/or newly synthesized proteins through ATP hydrolysis, which then contribute to the completion of mature protein confirmation process by recruiting ubiquitin ligases to target misfolded proteins and subsequently cleared by proteolytic process [31, 32].

Upon injury, the following causative factors like ions imbalance, oxidative stress, mitochondria dysfunction, apoptosis, cytotoxicity, necrosis, inflammation, and altered blood-brain permeability contribute to morphological and pathological modifications; most of the time, this aggravate medical conditions. Besides the above, the current availability of few well-demonstrated synthetics as well as semi-synthetic therapeutics for the management of NDs; but most of them exerted severe adverse effects [33]. The above-listed contributing factors suggest exploring other possibilities for the employment of novel screening and various other alternative neuroprotection approaches [34].

Main text

Natural medicinal plants have been widely used by traditional medical practitioners to treat various human illnesses [35–38]. Since research investigations on the development of new drugs are time-consuming and require a large capital investment, the focus is now being shifted to treatment strategies using herbal medicine obtained from various resources mainly from medicinal plants, which are plenty available and cost effective [39–41]. With the growing interest in advanced techniques, herbal medicine research, and medicinal plant, explorations are still considered to be a novel resource for new pharmacotherapeutic discovery and development [42]. However, isolation and development of clinically important drug leads from plants face enormous challenges [43] even after adopting high-throughput drug screening assays, because it is required to make extract compound libraries to screen biological activity [44, 45]. Despite having various challenges, NPs from herbal plants remain an indispensable constituent in the search for new drugs [40, 46, 47].

The bioactive principles or secondary metabolites pool symbolizes a constant main source for drug discovery and development [33, 48]. Hence, a detailed discussion on plant-derived important bioactive principles will be vital for developing new and novel therapeutics as they may amplify each other's activity with devoid of harmful side effects. Hence, traditional herbal research emphasizes aspects that warrant further investigation to establish its activity and utility for various diseases including neuro-protection and treatment. Although many herbal medicines are in place for the treatment of various NDs [49–53], still it is yet to be known how these compounds cure or alleviate many symptoms of NDs [54]. Moreover, these bioactive compounds, cellular targets, and their molecular mechanisms require detailed insight.

Neuro-protection means the mechanisms and approaches employed to protect the brain against various injuries of both acute and chronic NDs such as Parkinson's, Epilepsy, Dementia, Alzheimer's, etc. [55]. Traditional herbal therapeutics as well as nutraceuticals signify their vital importance in the prevention of NDs rather than the treatment [56, 57]. Although pathogenic mechanisms of numerous neurological disorders are not completely known, however, several results have highlighted key features of NDs based on the cues obtained from various neural disorder models as they mimicked most important characteristic features like mitochondrial dysfunction, oxidative load, neuroinflammation, etc. [58, 59]. Various investigative models have developed as an important tool to study neurotoxicity and symptomatic treatments. These methods have used as novel therapeutic strategies to assess these plant-derived compounds efficacy and their adverse effects [60].

Besides the above, many studies have described the neuro-protective properties of NPs by modulating numerous signaling cascades through direct effects on various cellular targets like kinases, numerous proteins including regulatory receptors [61, 62]. In addition, various results have also demonstrated other important pharmacological actions of NPs like chromatin remodeling and epigenetic modifications [63]. This broad spectrum of pharmacological properties has signified NPs as suitable therapeutic agents for the treatment of NDs/neurological disorders [64, 65].

Prospective role of medicinal plants in NDs

In recent times, the quest for novel therapeutics and their applications in the treatment of NDs more notably PD, HD, and AD gained enormous attention among investigators. Parkinson's disease incidence among aging population worldwide is increasing and considered as

second highest leading hetero-degenerative disease, dopaminergic neuronal degeneration in the substantia nigra of the basal ganglia region. Its hallmark features bring the following outcomes like rigid nature, developing balance loss together with other symptoms [66]. Protein deposits, also called Lewy bodies or cytoplasmic inclusions, are considered as one of the pathological characteristic feature, which are formed by the binding of α-synuclein to ubiquitin [67] causing dopaminergic neuronal degeneration [68]. Besides, PD has also been associated with several biochemical parameters, which include depletion of intracellular thiols, increased nigral iron content, and deficiency of mitochondrial complex I [69].

L-DOPA, a dopamine precursor (l-3, 4-dihydroxyphenylalanine), is the only therapeutic available to decreases the motor symptoms of PD, but it exerts side effects like dyskinesias [70]. To overcome the side effects caused by current medication and synthetic products, investigators have shifted their attention to various NPs. In this regard, several herbal plants/NPs including ginger, turmeric, pepper, and cloves with neuroprotective effects against PD have been reported [71, 72]. Besides, the consumption of green tea [73] and securinine obtained from *Securinega suffruticosa* are beneficial against age-related neurological problems by inhibiting NF-κB, mitogen-activated protein kinase (MAPK), and interferon gamma (IFN-γ) activity expression and reducing the activity of iNOS and NO level, thereby delay the onset of PD [74]. Huntington's disease (HD) or Huntington's chorea is inherent autosomal dominant NDs [75–77]. HD is characterized by personality changes, emotional imbalance, memory loss, the diminished capability to think clearly, weight loss, etc. [78–81]. Many beneficial therapeutic effects are attributed to medicinal plants to cure NDs, which include antioxidant, anti-apoptotic, and anti-inflammatory activities and neuronal function modulation [82, 83]. A growing number of medicinal plants are in use as a therapeutic for NDs including HD; they are *Centella asiatica*, *Gastrodia elata*, *Panax ginseng*, *Withania somnifera*, *Cannabis sativa*, *Ginkgo biloba*, *Bacopa monnieri* (BM), etc.

The following neuro-protective compounds, which include kaempferol, naringin, resveratrol, ginsenosides, curcumin, S-allylcysteine, and EGCG extracted from various herbal plants have employed to treat HD [50]. Among them, BM has proven its efficacy for HD as a potentially powerful antioxidant against oxidative damage instigated by neuro-toxicants and relieves stress-mediated neuronal impairment [84]. Besides, a few other plant-derived compounds like sesamol isolated from sesame oil, celastrol (triterpenoid quinine methide), and lycopene from tomatoes and tomato-based products used as antioxidants to treat HD [85] [86–89]. To support this, flavonoids also inhibit nitric oxide synthase (NOS) and hence delay HD progression [90–92]. Curcumin, a natural compound in turmeric, has inhibited motor defects and increased succinic acid dehydrogenase (SDH) function in 3-nitropropionic acid (3-NP)-induced neuronal disorders observed akin with HD patients [93, 94]. In addition, Resveratrol reversed 3-NP induced cognitive as well as motor defects [94, 95].

On the other hand, Alzheimer's disorder is considered as one of the severe and age-related chronic ND with the expectation of affecting nearly 107 million people by the year 2050 [96, 97]. It has the following characteristic features like impaired memory and cognitive function. The generation of amyloid-β (Aβ) fibrils is the hallmark pathogenesis of AD, which contains β-amyloid peptides. Though the precise mechanism of amyloid plaques generation is not clear, however, there are some plausible explanations given that Aβ normally formed and accumulated within the extracellular matrix (ECM) [98]. Few studies have also reported the therapeutic potential of nutraceuticals against Aβ plaques formation [49, 99]. Furthermore, numerous investigations have demonstrated the role of oxidative stress in AD patients' brains [100]. The antioxidant potential of some phytoconstituents like anthocyanins, carotenoids, etc. from *Arbutus unedo* plant has shown their greater antioxidant effects [101, 102]. Anthocyanins from *Vaccinium angustifolium* and resveratrol from *Vitis vinifera* have also demonstrated their alleviation action against oxidative stress-induced inflammation via stimulation of sirtuin-1 activity and decrease nuclear factor kappa B (NF-kB) expression [103].

Even though a huge number of evidence suggest that herbal plants offer a therapy for NDs, yet plenty of unidentified and unknown reservoir plants line up for exploration and proper investigation. Based on the available literature evidence including its neuroprotective action, *Ocimum basilicum* L may be qualified to be in this potential list. Therefore, we believe that the current comprehensive review may provide wealth of valuable information to serve as a resource for ethno medicine derived pharmotherapeutical discovery for the treatment of NDs. Among herbal plants, *Ocimum* species or known as basil which belongs to the Lamiaceae family is in use traditionally for a longer period to treat various illnesses [104]. The distribution of *Ocimum* species is commonly found in tropical regions of America, Asia, and Africa because of the favorable warm condition for their growth [105]. The reason for various geographic distribution as well as the generic variation of this genus is described by [106]. Numerous therapeutic properties of *Ocimum* species are due to the presence of certain bioactive compounds within the plants. There

are few important *Ocimum* species only investigated until now for their phytochemical screening or medicinal properties, which include *O. sanctum*, *O. basilicum*, *O. gratissimum*, *O. suave*, *O. americanum*, and *O. canum* [107].

O. basilicum L (Fig. 1) also called sweet basil with numerous vernacular names [108–110] is well practiced in various traditional healthcare systems [111–115]. *O. basilicum* plants were obtained from local plantation in Gombak, Kuala Lumpur, Malaysia and a voucher specimen (HF100) was deposited and plant authentication was done at the Herbarium, Bangi [116]. It has exhibited various pharmacological properties such as anti-ulcerogenic, anti-inflammatory, anti-microbial [117, 118], anti-asthmatic [119], and anti-carcinogenic/chemotherapeutic [120] activities. Besides, analgesic [121], anti-pyretic, anti-diabetic/hypolipidemic [122], digestive, hepatoprotective [123], anti-stress, and immunomodulatory [124], lipid lowering, and hypoglycemic [122, 125] activities of this potential plant is described in Fig. 2.

Bioactive principles and chemical composition of *O. basilicum* L.

Several studies have reported the major phytochemical composition of *O. basilicum* L. [122], which exhibited the presence of various phytoconstituents during the preliminary screening on the extract of *O. basilicum* in leaves including alkaloids, glycoside, gums mucilage, planteose, polysaccharides, proteins, amino acids, tannins, phenolic compounds, triterpenoids, steroids, sterols, saponins, flavones, and flavonoids. Besides the above, various other compounds such as tannins, saponin, alkaloids, phenolic compounds, flavonoids, glycosides, steroids, protein, and amino acids are also reported [126] except phenolic compounds. It is important to note that the extraction, isolation, as well as identification of chemical compounds are the crucial step. The presence of various phytocompounds within *O. basilicum* shows that different types of extraction methods affect its phytoconstituent detections and different parts of the plant exhibited different active compounds within the extract [110]. To support the above, leaves extracted by both hydro-distillation and *n*-hexane showed the presence of eugenol derivatives [127, 128] and high linalool content only by GC/MS analysis [129].

Fig. 1 *Ocimum basilicum* Linn

The unique aroma found in various species of *O. basilicum* is due to the presence and various compositions of their essential oils (EO). Seeds are rich in oil content and consist of varying concentrations and types like 50% linoleic acid, 22% linolenic acid, 15% oleic acid, and 8% unsaturated fatty acids. The following are the most prominent reported EO of basil α-terpineol, linalool, β-elemene, germacrene D, α-bergamotene, α-guaiene, eucalyptol, cubenol, τ-cadinol, eugenol, methyl eugenol, camphor, bornylacetate, α-caryophyllene, β-caryophyllene, elixen, β-cadinene [105, 121, 130]. But to a lesser extent, leaves have oleanolic acid and parts of ursolic acid, whereas dried leaves and flower tops contain essential oils other than protein (14%), carbohydrates (61%), high concentration of vitamin A and C, rosmarinic acid, and xanthomicrol [108]. Besides, flavonoid glycosides and aglycones as well as three different kinds of flavones like eriodictyol, eriodictyol-7-glucoside, and vicenin-2 have also reported. A study conducted by [131] found the variance among phenolic compounds and suggested that the difference may be attributed for different vegetation period. However, the presence of major components like caffeic acid and rosmarinic acid is observed in all the stages of plant growth. These findings suggest that the presence of rosmarinic acid as the most prevalent phenolic compound in *O. basilicum* L. Rosmarinic acid is one of the important phenolic compounds, which exhibit antiviral, antibacterial, anti-inflammatory, as well as antioxidant properties [132]. In addition, β-sitosterol (steroids), tannins, and polyphenols (2.2-2.3%) have reported in *O. basilicum* L. Figure 3 shows molecular structure of rosmarinic acid a representative candidate of *O. basilicum* L.

Numerous confirmative investigations on drug discovery and development, mostly on medicinal plants, have demonstrated their neuroprotective efficacy through numerous cellular and molecular signaling pathways on different types of NDs [133]. In this regard, [134] reported that many kinds of chemical constituents (e.g., diterpenes and cyclodepsipeptides) identified as key components to interact with the GABAA receptor

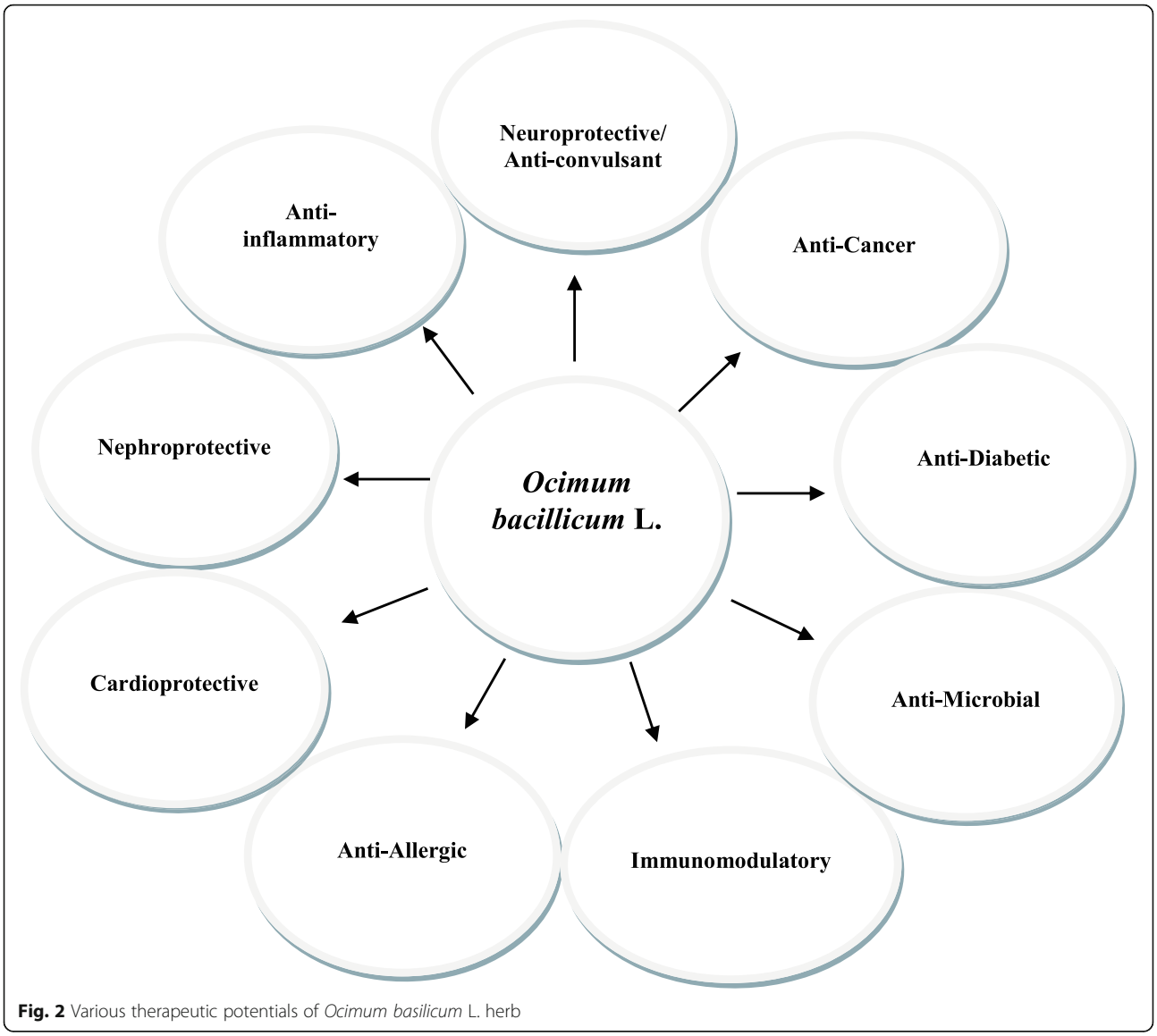

Fig. 2 Various therapeutic potentials of *Ocimum basilicum* L. herb

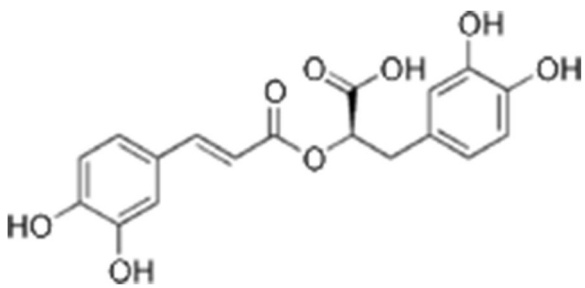

Fig. 3 Structure of Rosmarinic acid ($C_{18}H_{16}O_8$), a representative prominent bioactive principle of *O. basilicum L*

selectively inhibit its activity [135]. In addition, alkaloids firmly regulate the interaction of bioactive principle muscimol with GABA receptor complex [136, 137]. Similarly, some phytochemicals like flavonoids also proven their binding ability on the GABAA receptor specifically at the benzodiazepine site [138, 139] and established as a scavenger against pro-inflammatory and neurotoxic radical species [140]. Moreover, many medicinal plants such as *Mentha arvensis*, *Arisaema amurense*, *Salvia miltiorrhiza*, *Glycyrrhiza uralensis Biota orientalis*, *Albizia julibrissin*, and *Astragalus membranaceus* have proven their inhibitory efficacy on monoamine oxidase-B (MAOB) enzyme [141].

Previous results obtained from various experimental results found that α-asarone, a compound isolated from *Acorus gramineus*, exhibits its anti-convulsing, antileptic, as well as sedative action in the hippocampus of

CNS by increasing tonic GABAergic neuronal activity [142, 143]. Besides, the abundance of natural polyphenol especially flavonoids present in fruits and other cruciferous vegetables exhibited their anti-inflammatory, antiseizure, and antiepileptic activities by modulating allosteric GABAA receptors in pentylenetetrazole-induced seizure model animal studies [144, 145]. To support this, naringenin 4'7-dimethyl ether has also shown its effectiveness against various types of available acute seizure mice models like 6 Hertz (Hz) psychomotor seizure model and timed intravenous pentylenetetrazole convulsive seizure model [146]. Thus, it clearly shows that the naringenin methylation process has augmented the efficiency of anti-leptic actions against various seizure models.

Several *Ocimum* species have been investigated for their medicinal properties [147–150]. Figure 4 depicts some of the important therapeutic properties and preventive mechanisms. To support this, the aqueous extract derived from *O. basilicum* L. and its flavonoids, orintin, apigenin, carnosic acid, vicenin, and eugenol have shown to protect γradiation-induced mortality in mice but selectively protect the normal tissues [148, 149]. In addition, *Ocimum* spp. containing EO-rich phenolic compounds and anthocyanins exhibit wide spectrum of therapeutic use [151, 152]. Many studies have isolated EO from *O. basilicum* L. and reported its various prominent volatile components [153–157]. These compounds have demonstrated anticonvulsant effects [158] and CNS depressant activity [159] in pentylenetetrazol-induced animal model seizures but not in the strychnine-induced seizures. Moreover, the action of EO was reversed by flumazenil (agonist of GABAA receptor) corroborate the results that *O. basilicum* L. EO exerts its anti-convulsing action by specifically targeting GABAAergic mechanism [133, 160]. Normally, strychnine antagonizes glycine receptor activity by stimulating convulsions and enhances post-synaptic excitability and subsequent activities in the brain stem and spinal cord without involvement of GABA receptor [161].

Despite knowing the pathogenesis of NDs in the specific region of the brain, the poor antioxidant defence system together with the excessive ROS generation are unifying distinct factors responsible for progressive neuronal death [18, 162]. Simultaneously, a growing interest on the neuroprotective and antioxidant potentials of herbal supplements, medicinal plants, which include *O. basilicum L* and their bioactive principles require further exploration and detailed discussion on specific cellular and molecular mechanisms. In this regard, rosmarinic acid obtained from *Rosmarinus officinalis* and *Ocimum* species strongly exhibited its action against oxidative molecules [163] by inhibiting lipid peroxidation and maintaining cell membrane integrity without altering cell structures [164]. The neuroprotective efficacy of rosmarinic acid (100 mg/kg) was demonstrated using Kainic acid-induced (agonist of AMPA/KA receptor) temporal lobe epilepsy in rats [165–167] and ethanol-induced geno-toxicity in mice [168]. In vitro studies employing rosmarinic acid in N2A cells have also shown the similar neuro-protective properties [169].

In addition, cells treated with rosmarinic acid exhibits concentration-dependent protective properties in hydrogen peroxide (H_2O_2)-induced oxidative stress by reducing ROS generation and cell loss [170–173]. The actions were similar to caffeic acid and shown its neuroprotective action by enhancing learning and memory in the inhibitory avoidance tasks (avoiding specific tasks) by reducing acetyl cholinesterase (AChE) level [174–176]. Furthermore, a observation has also revealed the neuroprotective actions of rosmarinic acid, which are mostly evident by the upregulation of protective genes, brain-derived neurotrophic factor (BDNF), tyrosine hydroxylase (TH) levels, and prevent mitochondrial dysfunction [169]. In line with this, eugenol, another important phytocomponent present in EO of *O. basilicum* and other species of *Ocimum* and clove oil [177, 178], has shown strong antioxidant activities [179] and exhibiting reduced level of calcium and AChE activity [178]. Furthermore, EO has shown to reduce neuronal loss and lactate dehydrogenase enzyme release in *N*-methyl-D-aspartate (NMDA)-induced neurotoxicity [180, 181].

Though previous results have demonstrated that individual compounds of *O. basilicum* have shown their neuroprotective efficacy in numerous neurodegenerative animal models; however, one can possibly expect an alternative approach of employing crude extracts or applying combination of bioactive principles for the NDs treatment. By adopting this approach, many signaling mechanisms including antioxidant activity enhanced and mediated by the synergism efforts. Besides, *O. Basilicum*-derived phytocompounds prevent cerebral ischemia, reperfusion, and short-term memory loss and improve motor performance [173–175]. Results of above investigations suggest that the neuro-protection may be owing to the existence of tannins, phenols, and flavonoids [182]. To support this, mice administrated with the extract of *O. basilicum* at the concentration ranging from 200 to 400 mg/kg for 7 days reversed the scopolamine-induced memory loss when compared to other drug standard drug tacrine. These reversal behavioral actions accompanied by reduced acetyl cholinesterase (AChE) and thiobarbituric acid reactive substances (TBARS) and increased glutathione levels in both the cortex and hippocampus. In addition, focal gliosis, increased vacuolation, and lesser number of pyramidal cells were also evident.

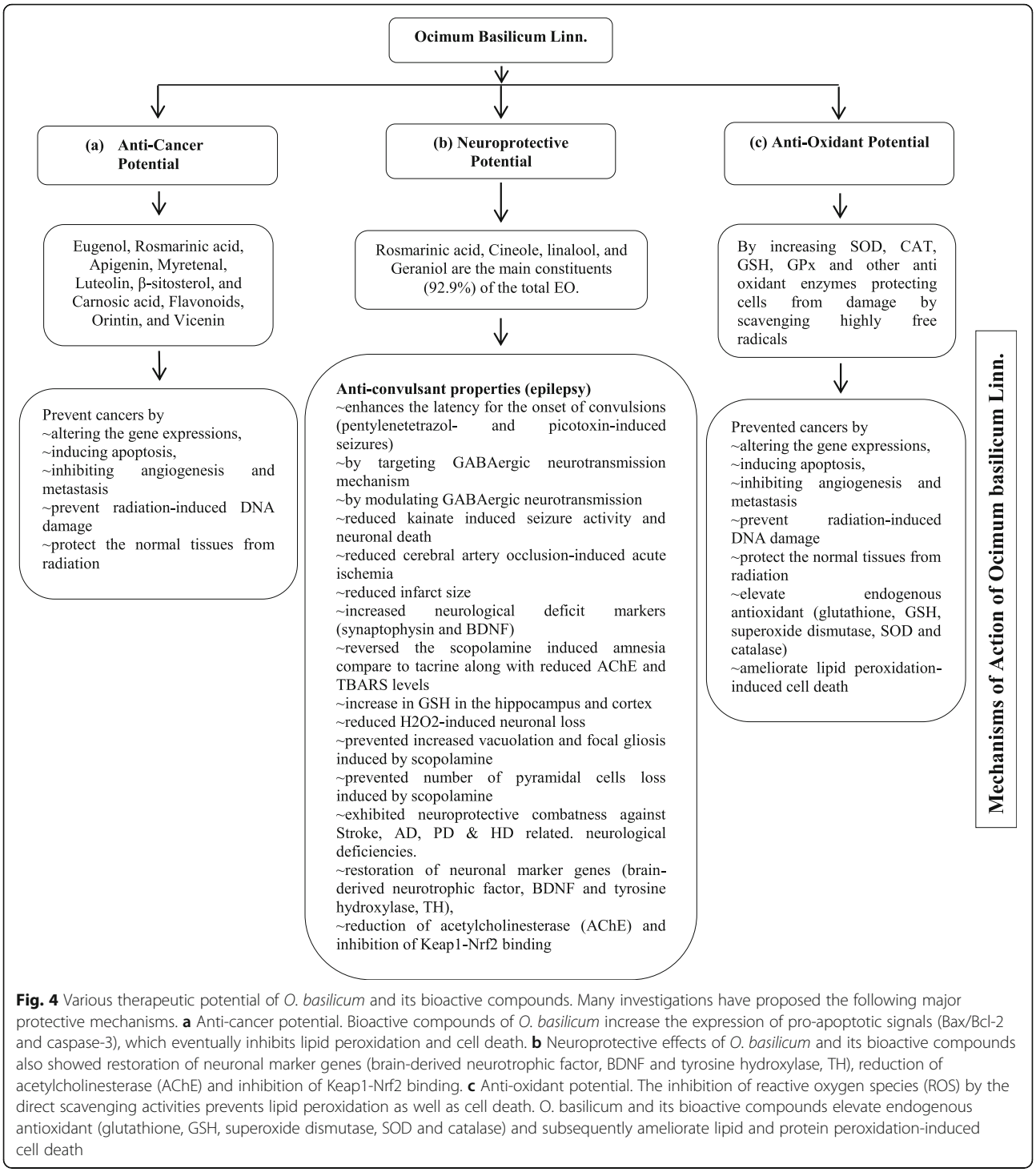

Fig. 4 Various therapeutic potential of *O. basilicum* and its bioactive compounds. Many investigations have proposed the following major protective mechanisms. **a** Anti-cancer potential. Bioactive compounds of *O. basilicum* increase the expression of pro-apoptotic signals (Bax/Bcl-2 and caspase-3), which eventually inhibits lipid peroxidation and cell death. **b** Neuroprotective effects of *O. basilicum* and its bioactive compounds also showed restoration of neuronal marker genes (brain-derived neurotrophic factor, BDNF and tyrosine hydroxylase, TH), reduction of acetylcholinesterase (AChE) and inhibition of Keap1-Nrf2 binding. **c** Anti-oxidant potential. The inhibition of reactive oxygen species (ROS) by the direct scavenging activities prevents lipid peroxidation as well as cell death. O. basilicum and its bioactive compounds elevate endogenous antioxidant (glutathione, GSH, superoxide dismutase, SOD and catalase) and subsequently ameliorate lipid and protein peroxidation-induced cell death

Meanwhile, oxidative stress is an important death signal contributor of NDs by causing cell death or apoptosis [18]. Free radical stress occurs when oxidant level is more with diminished antioxidant defence system found in our body. Though natural antioxidant enzymes such as SOD and glutathione (GSH) are available in our body, yet the exogenous antioxidants are still required through diets. Rather than antioxidant, antimicrobial, as well as antitumor, the extract of *O. basilicum* L. also showed neuro-protective effects which generally beneficial to combat neurological deficiencies such as Stroke, Alzheimer's, Parkinson's, as well as Huntington's disease. Singh et al. [182] demonstrated that pre-treatment of ethyl acetate extract of *O. basilicum* Linn. on mice could

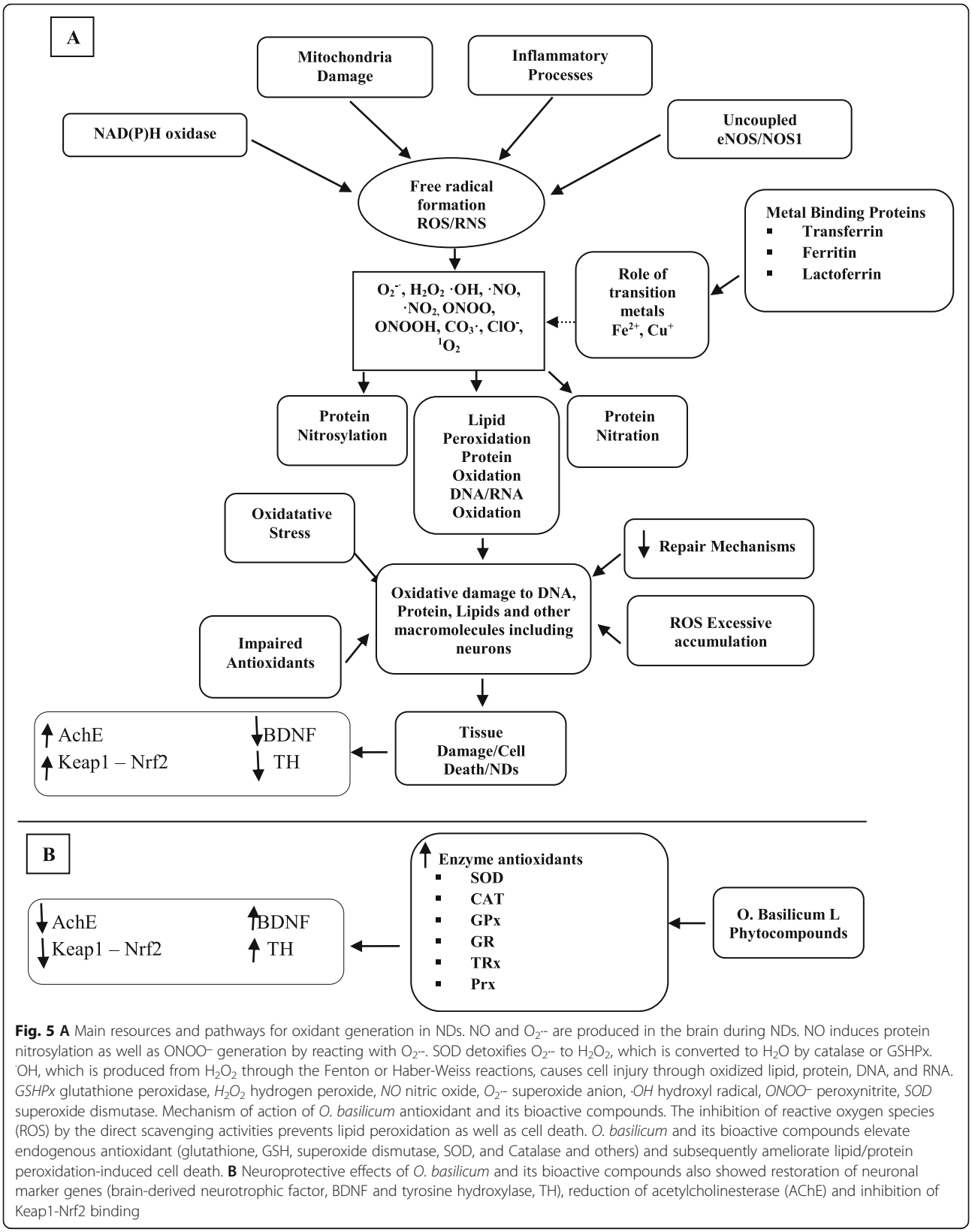

Fig. 5 A Main resources and pathways for oxidant generation in NDs. NO and O_2·- are produced in the brain during NDs. NO induces protein nitrosylation as well as $ONOO^-$ generation by reacting with O_2·-. SOD detoxifies O_2·- to H_2O_2, which is converted to H_2O by catalase or GSHPx. ·OH, which is produced from H_2O_2 through the Fenton or Haber-Weiss reactions, causes cell injury through oxidized lipid, protein, DNA, and RNA. *GSHPx* glutathione peroxidase, H_2O_2 hydrogen peroxide, *NO* nitric oxide, O_2·- superoxide anion, *·OH* hydroxyl radical, $ONOO^-$ peroxynitrite, *SOD* superoxide dismutase. Mechanism of action of *O. basilicum* antioxidant and its bioactive compounds. The inhibition of reactive oxygen species (ROS) by the direct scavenging activities prevents lipid peroxidation as well as cell death. *O. basilicum* and its bioactive compounds elevate endogenous antioxidant (glutathione, GSH, superoxide dismutase, SOD, and Catalase and others) and subsequently ameliorate lipid/protein peroxidation-induced cell death. **B** Neuroprotective effects of *O. basilicum* and its bioactive compounds also showed restoration of neuronal marker genes (brain-derived neurotrophic factor, BDNF and tyrosine hydroxylase, TH), reduction of acetylcholinesterase (AChE) and inhibition of Keap1-Nrf2 binding

prevent neuron injury in mice induced by reperfusion cerebral damage. Reperfusion-injury introduces oxidative stress among mice, which is one of the mechanisms for neuro-degeneration diseases. Figure 5 describes the main resources and pathways for oxidant generation in NDs and *O. basilicum* and its bioactive compounds antioxidant mechanisms and neuro-protective effects. Many extensive reports suggest that *O. basilicum* Linn. a traditionally grown medicinal herb may become a potential therapy for NDs by acting as a neuro-protective agent, since it possesses antioxidant properties, which could help to prevent oxidative stress by scavenging the oxidation reactions and hence avoid cell apoptosis and cell death.

Conclusions

Although there has been great advancement in understanding the etiologies of most NDs, but no complete remedies or cure for them yet. However, many extensive attempts have been made to understand the pathophysiology of these diseases along with the available treatment interventions to discover new therapeutic options for NDs. NDs complicated nature with a substantial memory loss and quality of life especially among elderly patients occurring frequently in the developed nations but the same trend also witnessed recently in developing countries world-wide. Besides, current therapeutic regimens are also not effective for these problems because of their poor clinical outcome. Despite the world has witnessed tremendous advancement on the current therapeutics availability for the management of NDs, still the field is in its infancy, in terms of research efforts, in adequate outputs, and resource utilization. However, on the positive side, the application of traditional medicinal herbs have increased in recent years and contributed their righteous share for NDs treatment. By adapting multidisciplinary multi-center research approaches with the inclusion of appropriate clinical trials using bioactive principles may provide potential solutions to address and manage this severe complex disease.

In summary, many plant extracts have been shown as a promising source of novel drug discovery by traditional medical practitioners for years to cure various diseases. Among these plants, the *Ocimum* species have been known worldwide as a potential herb with numerous health benefits. This review revealed the genus of *Ocimum*, some therapeutic potential of *Ocimum* species, which mainly focused on *O. basilicum* Linn. and its phytocompounds. So far, only a limited number of secondary metabolites have been identified within *Ocimum* species. Hence, further investigations are required on various known and unknown bioactive principles of *Ocimum* species, which include *O. basilicum* L. Since these biological constituents are highly valuable to the pharmaceutical industries in formulating new drugs for various disease treatment. Finally, the authors conclude that this plant may serve as promising therapeutics for the treatment of NDs.

Abbreviations

NDs: Neurodegenerative diseases; SOD: Superoxide dismutase; GSH: Glutathione; AChE: Acetyl cholinesterase; TBARS: Thiobarbituric acid reactive substances; NMDA: *N*-methyl-D-aspartate; TH: Tyrosine hydroxylase; BDNF: Brain-derived neurotrophic factor; H_2O_2: Hydrogen peroxide; ROS: Reactive oxygen species; AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; KA: Kainic acid; GABA: Gamma aminobutyric acid; CNS: Central nervous system; EO: Essential oil; MAOB: Mono-amine oxidase-B; GC-MS: Gas chromatography–mass spectrometry; NF-kB: Nuclear factor kappa B; APOE-ε4: Apolipoprotein E; AD: Alzheimer disease; PD: Parkinson's disease; HD: Huntington's disease; IFN-γ: Interferon gamma; MAPK: Mitogen-activated protein kinase; L-DOPA: l-3,4-Dihydroxyphenylalanine; PUFAs: Polyunsaturated fatty acids; APP: Amyloid protein precursor; PSEN 1, 2: Presenilin-1, 2

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Plant authentication

O. basilicum plants were obtained from local plantation in Gombak, Kuala Lumpur, Malaysia and a voucher specimen (HF100) was deposited and appropriate plant authentication was done at the Herbarium, Bangi by a co-author NA.

Authors' contributions

MAS inscribed the major part of the manuscript contributed to the guiding and configuring of the manuscript. SA, NA, FMA, AIA, OAZ, and YH contributed to the writing of the manuscript in various segments. All authors have read and approved the manuscript.

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