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Literature Evidence and Arrive Assessment on Neuroprotective Effects of Flavonols Quercetin, Rutin and Isoquercitrin in Neurodegenerative Diseases'Models

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Abstract

This paper was based on a literature search of PubMed and Scielo databases using the keywords ?Flavonoids, Neuroprotection, Quercetin, Rutin, Isoquercitrin, Alzheimer, Parkinson, Huntington? and combinations of all the words. We collected relevant publications, during the period of 2000 to 2016, emphasizing in vivo and in vitro studies with neurological assessment of flavonol?s potentials, as well as classifying studies according to evidence levels, in order to elucidate evidence-based literature and its application on clinical research. In addition, we highlight the importance of flavonols in modern research fields, indicating their neuroprotective potential and use thereof as preventive and therapeutic treatment of numerous neurodegenerative disease. Neurodegenerative diseases, such as Alzheimer39;s disease, Parkinson39;s disease and Huntington39;s disease, represent worldwide a major health problem with great financial impact. They are multifactorial diseases, hallmarked by similar pathogenesis that covers conditions such as oxidative stress, formation of free radicals, abnormal protein dynamics (degradation and aggregation), mitochondrial dysfunction, lipid peroxidation and cellular death or senescence. Flavonols are polyphenolic compounds, widely distributed in the plant kingdom and found in high concentrations in vegetables, fruits and teas. Their neuroprotective effects are mainly related to their antioxidant, anti-proliferative and anti- inflammatory properties. It was this paper?s intention to contribute with an evidence analysis of recent studies approaching neuroprotective effects of flavonols and the potential to conduct human clinical studies.

Index terms—

I. Introduction lavonoids represent one of major polyphenolic groups, which are widely distributed in the plant kingdom and commonly found in vegetables, fruits and teas of the human diet 1 . These compounds have shown low toxicity as well as a variety of physiological effects 1 . In the past few decades, these naturally occurring compounds have attracted much attention by reported beneficial effects on health, such as antioxidant, antitumor, anti-inflammatory and anti-allergic effects 2 , as well as presenting low toxicity to human organism 1,3 . In midst the various classes of flavonoids, the flavonols have been the focus of many in vitro and in vivo studies for their diversified actions on numerous biological pathways 1 . Structurally, flavonoids are composed of a basic flavylium cation, with three phenolic rings 4 . Flavonols present subtle molecular changes to the main ring (Ring C), with the addition of a hydroxyl group (OH) on the third carbon, and a carbonyl group (C=O) on carbon fourth 1,5 . Many reports have shown that structure changes of flavonoid molecules result in variations of bioavailability, by changing absorption efficiency and pathways; thus, also altering biological effects and creating action mechanisms specificity 1,4,[6][7][8] .

Flavonoids neuroprotective effects are mostly bound to its related antioxidant, anti-proliferative and anti-inflammatory properties 9,10 . The Central Nervous System (CNS) is highly exposed to oxidative damage, due to high oxygen consumption, high levels of unsaturated lipids and presence of transitional metals 1 . In addition, because of inefficient antioxidant defense mechanisms, alterations of neuronal organic homeostasis can cause grave repercussions 1,9 . Antioxidant properties are correlated since oxidative stress and lipid peroxidation have been linked to a range of neurological pathologies, such as brain trauma, ischemia and neurodegenerative disorders 2,11,12 . Thus, flavonoids ability to scavenge ROS and inhibit lipid peroxidation, protecting neuronal cells from oxidative damage, may be used to prevent and treat neurological pathologies 2 .Neurodegenerative disorders, such as Alzheimer, Parkinson's and Huntington's disease cause a progressive functional alteration of neuronal systems 13 . Worldwide, they present variable incidence and constantly relate to high morbidity rates, higher cost in health care and social impairment [13][14][15] . These pathologies have been well studied; however, new advances in physiopathology and, therefore, in therapeutic modalities are infrequent, maintaining no cure or reversible treatments.

Other flavonoids, such as resveratrol, fisetin and hyperin have also been considered as potential drugs with neuroprotective effects 9,13,[16][17][18][19][20][21][22] . Recent studies verified, different flavonoids act on specific organic pathways 1 , yet comparable studies between flavonoids are rare. Resveratrol, as an example, has shown neurological and cognitive enhancement properties in a clinical trial 23 . Quercetin and rutin have been widely investigated as therapeutic drugs, especially concerning anti-proliferative and antioxidant effects, for many diseases, including CNS pathologies. However, neuroprotective potential of flavonoids in human trials has been poorly addressed, and Isoquercitrin has rarely been implied in studies investigating neuroprotective effects and comparison studies of the same subject.

1 II. Methods/Research

2 b) Literature Evidence

Evidence Based Medicine (EBM) is a systematic analysis of present-day research and scientific findings, in which obtained information is classified by authenticity and Evidence Level results 24 .

Thus creating a hierarchy system to evaluate information and incorporate in a practical environment of research, as well as to support the conduct of clinical care and therapeutic options 25 . Recommendation levels are the results of extensive research analysis and an important guide to practitioner's clinical decisions 26 . Although animal experiments have always contributed to our understanding of drug action mechanisms and pathophysiological aspects of many diseases 27 , some authors debate on whether animal researches are valuable predictors of human conditions and pathogenesis, due to interspecies differences and lack of uniform requirements for reporting animal data and comparable results 28 . Considering the pyramid of medical research, animal experimentation and in vitro studies take their place at the bottom, reflecting basic studies; however, tools of assessment of these studies have emerged in the last decade to improve transparency and accuracy of reports 29 . One of which, ARRIVE guidelines (Animals in Research: Reporting in Vivo Experiments)creates a checklist of 20 steps to be met during animal experimentation reports 29 . Although ARRIVE checklist is not mentioned in many animal reports, in the past five years endorsement of this tool amongst journals has risen considerably 30 , becoming an important source of evaluation. Thus, it was this paper's intent to grade Animal Experimentation and In Vitro Studies´ Evidence Level, through a personal classification (Table 1), derived from the Oxford Centre for Evidence Based Medicine (CEBM). In addition, apply the ARRIVE checklist toin vivo animal studies referenced in this paper.

3 c) Flavonoids

Flavonoids represent one of major polyphenolic groups, which are widely distributed in the plant kingdom and commonly found in vegetables, fruits and teas of the human diet 1 . Recent experimental studies and clinical trials conducted with flavonoids, in particular the class of flavonols, have demonstrated a wide variety of physiological effects, including antioxidant, antiproliferative/antitumor and anti-inflammatory, also correlating some of their action mechanisms to neuroprotective potential. Thus evidencing this class of molecules as an accessible alternative of preventive therapy or treatment of numerous neurological diseases. Flavonoids can be found in nature as aglycone forms, glycosides or methylated/acylated derivatives 1 . Amongst flavonols representatives, the best-known molecules are (1) Quercetin, an important aglycone form and a pioneer subject mid flavonoid research; (2) Rutin, main hydrophilic glycoside molecule; and (3) Isoquercitrin (IQ), main lipophilic glycoside, also known as quercetin-3-O-glucoside (Q3G) and Isoquercetin, a nearly identical quercetin-3-monoglucoside 1,31 .

Flavonoids absorption occur predominantly in the small intestine, however it is limited by molecular weight and hydrophilicity 1,31 . Few studies have been conducted as to elucidate bioavailability and absorption across the blood-brain barrierin human models 32,33 (Evidence Level 1B), whereas most studies have used in vivo animal models, biological differences and lack of complete physiological understanding of flavonoid's absorption in the small intestine,have limited new findings. Nevertheless, the type of sugar moiety attached to primary aglycone molecule, has been named the major determinant of small intestine absorption, rather than its position in the same molecule 34 .

In food plants, quercetin occurs almost exclusively as glycosides, in which the and the dominant type of glycoside vary amongst foods and is usually located at the 3 or 4 position of the pyrone ring 1,34 . Onions, kale, broccoli and apples are important sources of glucoside molecules, such as Rutin 35 . IQ is a common naturally occurring glycoside also obtained by enzymatic hydrolysis of rutin with hesperedinase, an enzyme produced by specific types of fungisuch as Penicillium sp.

Heperedinase has a ?-l-ramnosidase selective activity when applied at 58°C for 30 minutes, capable of cleaving the rhamnosidase radical of rutin's basic structure and leaving the glucoside radical intact, transforming it into IQ 36 . This procedure, generates what is called enzymatic modified IQ or Hydrolysed Rutin (HR), both of which consists of a mixture that includes IQ (69,5%), quercetin (7,5%), rutin and other small metabolites 36 . Studies have shown the superiority of anti-oxidant and anti-proliferative properties of HR when compared solely to quercetin and rutin (Evidence Level 2C) 36,37 .

4 III. Neurodegenerative Diseases

Neurodegenerative diseases are a consequence of genetic and environmental factors that are strongly associated with age 38 . These disorders arise from multifactorial conditions that interfere directly with cellular oxidative homeostasis and function **??**8 . Amongst various pathophysiological factors, increased oxidative stress, mitochondrial dysfunction and abnormal protein dynamics represent a common role in the development of different neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) **??**8 . Also appearing to command numerous neuronal pathways, leading to alterations in neurotransmission and ionic channels, protein aggregation, impaired bioenergetics and even cellular death **??**8 .

Free radicals are indispensable molecules to cellular function by involvement in many biochemical activities 39 . However, oxidative stress arise from disturbances between pro-oxidant/antioxidant equilibrium 39 . Overproduction of free radicals produce cytotoxicity and genotoxicity by damaging biomolecules, such as proteins, lipids and DNA 39 and leading to arise of various chronic diseases, including in the CNS 39 . In the brain glial and neuronal cells are particularly sensitive to free radicals and actively targeted by ROS 39 . Primary neuroprotective potential of flavonoids rely mainly on their antioxidant effect and leading mechanism of action seems to be reduction of cellular oxidative stress by scavenging and decreasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) in brain tissue(Evidence Level 2C) 2,9,[40][41][42][43] . Also exhibiting activation of anti-oxidant enzymes (Evidence Level 1B) 44 (Evidence Level 2C) 45,46 , protein disaggregation and diminished production (Evidence Level 2C) 47 , decrease of lipid peroxidation (Evidence Level 1B) 48 (Evidence Level 2C) 42 , transitional metal chelation (Evidence Level 2C e 4) 2,49-51 and antiinflammation effects (Evidence Level 1B) 52 . Although, Ansari et al. (2009) demonstrated in an in vitro study that quercetin showed dual effect on oxidative stress; at lower dosages, antioxidant effects were observed, though in higher dosages, it exhibited a pro-oxidant effect also increasing neuronal dysfunction, it is still clear flavonoids present oxidative-protective effects on various diseases, including those of the CNS.

5 a) Alzheimer's Disease

Alzheimer's disease (AD) is a complex neurological disorder clinically characterized by progressive loss of memory and cognition; histopathology demonstrates accumulation of extracellular ?-amyloid plaques (major constituent of senile plaques), intracellular neurofibrillary tangles, tau protein phosphorylation and neurodegeneration of synaptic neurons, especially in the hippocampus 13,53 .Oxidative stress and neuroinflammation are also considered hallmarks of AD, mainly responsible for increasedneurotoxicity 54 of cognitive-modulating areas 55 . In addition, the decrease in cholinergic neurotransmission has also been implicated in cognitive decline and behavioral changes of AD 56 .

Flavonoids represent an interesting class of phytochemicals and, even before scientific studies, have been widely used as phytotherapy medicines, like Ginkgo biloba, which includes quercetin and kaempferol 57 . In 2009, Shi et al. demonstrated quercetin molecule was responsible for high antioxidant activity of this plant extract, corroborating to the hypothesis of flavonoids, in particular flavonols, as possible therapeutic drugs with neuroprotective potential (Evidence Level 2C) 58 .

A main pathophysiological mechanism of AD is the transformation of ?-amyloid peptides into amyloidbeta (Abeta) plaques and the extracellular aggregation of plaques in areas such as the hippocampus 47 , which appear to be an early phenomenon and is currently used as a diagnostic tool of the disease through PET scan markers (Evidence Level 2A) 59 . In the last few years, some studies have comprised flavonoid's neuroprotective potential and investigated antiamyloidogenic properties. Ansari et al. (**??**009) demonstrated quercetin's protective effect under low dosages (5 ?M and 10 ?M), strongly inhibiting Abeta fibril formation and preventing glutathione oxidation (Evidence Level2C) 60 . In 2011, Jimenez-Aliaga evaluated anti-amyloidogenic potential of both quercetin and rutin, demonstrating inhibition of Abeta fibrils formation and disaggregation by both compounds, however, noticing statistical superiority of quercetin's effects. Also reporting the reduction of ROS production and lipid peroxidation index (Evidence Level2C) 47 . In addition, Choi et al. (2014) studied thein vitro activity of a flavonoid panel, including quercetin and rutin, against Abeta-induced toxicity. Results corroborated previous studies showing that flavonoids significantly block A?induced neuronal toxicity(Evidence Level 2C) 61 .

Liu et al., 2013 investigated in vivo the protective effects of quercetin against Abeta-induced toxicity, on both endothelial cells and neurons, after oral administration of quercetin for a period of 8 days; learning and memory were evaluated by Morris Water Maze test, and cerebral flow was closely monitored. Results showed neurovascular coupling protection, with reduction of oxidative stress and maintenance of neurovascular unit(Evidence Level 1D) 62 .

Recent in vitro and in vivo studies investigated neuroprotective effects of quercetin on Abeta-induced toxicity models. Results showed quercetin improved cell viability, by diminishing neuronal and endothelial oxidative stress(Evidence Levels 2C, 1D) 63,64 , and the production of ROS and LDH were decreased, as an increase on superoxide dismutase occurred (Evidence Level2C) 63 . Mohebali et al., 2016 demonstrated both Rutin's and Quercetin's potential to down regulate inflammation-involved genes in AD(Evidence Level 1D.I) 65 . Moreover, Sabogal-Guáqueta et al., performed an in vivo study with quercetin (25mg/kg) i.p. administration, for 3 months,on triple transgenic AD model mice, observing a decrease of extracellular ?-amyloid deposition, as well as a reduction of tau phosphorylation, astrogliosis and microgliosis in the hippocampus and amygdala(Evidence Level 1D) 66 .

Isolated, rutin has been less studied in AD over the years. In 2012, Javed et al. conducted the investigation of rutin's neuroprotective antioxidant effects in an in vivo intracerebroventricularstreptozotocin (ICV-STZ) induced toxicity model. Rutin was pre-administered orally (25mg/kg) for 3 weeks, and results indicated attenuation of STZ-induced inflammation by reducing the expression of cyclooxygenase-2 (COX-2), interleukin-8 (IL-8) and nuclear factor-kB, thus preventing neuro-inflammatory morphological changes in the hippocampus(Evidence Level 1D) 67 .

In addition, recent studies that comprised rutin's antioxidant activity on Abeta-induced neurotoxicity showed the decrease of ROS and RNS as the main action mechanism, consequently reducing lipid peroxidation. Interestingly, rutin was also capable of diminishing glutathione levels and dependent enzymes, also downregulating astrocytosis and microgliosis and, therefore, proving to having similar effects to quercetin (Evidence Levels 1D) [68][69][70] .

Another hallmark characteristic of AD is the decrease in cholinergic neurotransmission, which has been implicated in cognitive decline, leading to dementia, and behavioral disorders 56 . The increase on cholinergic neurotransmission is an important focus of recent drug therapy and comprises the inhibition of acetylcholinesterase (AchE), acetylcholine's degrading enzyme 71 . Both quercetin and rutin have been targets of recent studies focusing on AchE inhibition, since it is an important target on Alzheimer's drug therapy. Quercetin is a strong AchE inhibitor(Evidence Levels 1D, 2B.II) 72,73 , presenting higher binding strength to active site of the enzyme then some of the drugs in the market, like Donezepil 74 ; also acting in a dose-dependent manner(Evidence Level 3B) 42 . Rutin also seems to show AchE inhibition properties(Evidence Level 3B) 75 ,however no study has solely involved this compound. There are no studies indexed on PubMed or Scielo involving isoquercitrin's specific neuroprotective effects in AD. Nevertheless, IQ exhibits important antioxidant activity 76 and has been implied as a promising molecule for the treatment of several pathologies, especially cancer 77 .

6 b) Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative movement disorder mainly characterized by progressive loss of dopaminergic neurons within nigrostriatal pathway, affecting substantia nigra area, and associated with microglial-mediated neuro-inflammation 22 . Pathogenic aspects of PD involve mitochondrial dysfunction, changes in micro-RNA and ?-synuclein levels 13 , a major constituent of Lewy bodies and a hallmark of PD 78 A associated as a risk factor for dopamine cellular degeneration of PD 79 , and mitochondrial dysfunction plays an important role on energetic balance as well as regulating oxidative and apoptotic pathways **??**8 .

Quercetin has been widely investigated for its antioxidant effects; however, specific PD model investigations are scarce. On chronic rotenone (ROT)induced parkinsonian models quercetin (25-75mg/kg i.p.) showed reduced loss of ROT-induced dopaminergic neurons, also decreasing glutathione levels and increasing anti-oxidant enzymes (catalase and superoxide dismutase)(Evidence Level 2B) 80 . In 2015, Denny Joseph et al., also investigated on ROTinduced models the beneficial effects of treatment association between fish oil and quercetin. Results corroborated previous studies demonstrating significant behavioral change as well as attenuation of oxidative stress and mitochondrial dysfunction indicators (Evidence Level 1D) 81 .

Other studies using methyl-4-phenylpyridinium ion (MPP(+)), a parkinsonian toxin that provokes degeneration of dopaminergic neurons 82 , and 6hydroxydopamine (6-OHDA), a selective dopaminergic neurotoxin 83 . Also demonstrated quercetin's neuroprotective potential by reducing apoptotic neuronal death, through modulation of pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) genes, and decreasing oxidative stress and neuro-inflammation (IL-1, TNF-? and COX-2) on microglial cells (Evidence Levels 2C, 2C, 1D, 1D) [82][83][84][85] . Although these results are consistent with literary review appointing quercetin as an antioxidant molecule, some studies have shown a paradoxical effect of this compound when used in high dosages (Evidence Level 2C) 60 .

In addition, in 2015, Ahn et al. investigated quercetin's specific effect on ?-synuclein expression. During the experiment, PC12 cells were pre-treated with quercetin and results showed quercetin presents neuroprotective effects affecting various mechanisms such as apoptosis and oxidative stress; however, quercetin treatment increased ?-synuclein levels, and although cell viability and survival were unaltered with the up-expression, this data suggests quercetin's effects on PD is still not entirely understood(Evidence Level 2C) 78 .

During the course of 2014 to 2016, Magalingam et al., produced a series of three articles investigating Rutin and Isoquercitrin on 6-OHDA PD-induced models. Both rutin and IQ demonstrated antioxidant effects by reducing lipid peroxidation and increasing anti-oxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) (Evidence Level 2C) [86][87][88] . Cytoprotective activity of IQ occurred in a dosedependent manner. Furthermore, Rutin showed upregulation of the TH gene, an important factor in dopamine biosynthesis; as well as modulation of apoptotic pathways by reducing Park2, Park5, Park7, Caspase 3 and Caspase 7 genes(Evidence Level 2C) 86 .

7 c) Huntington's Disease

Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder clinically characterized by motor, cognitive and behavioral impairment, also presenting high morbidity and mortality rates 89 . Incidence is higher at European countries and mean age of symptoms onset occurs around 40 years old 90 . HD is cause by an expanded CAG trinucleotide repeat in the HTT gene, responsible for encoding the protein huntingtin. The mutation lead to the production of an abnormal protein with long polyglutamine sequences that confers toxic properties and predisposes protein fragmentation, which can result in neuronal death 91 .

Quercetin is the only major flavonol whose neuroprotective effect has been associated to Huntington's disease treatment potential. In this review, we found no articles investigating rutin or isoquercitrin effects on HD models. In 2013, Sandhir et al. evaluated oral supplementation of quercetin (25mg/kg) on 3nitropropionic acid-induced (3-NP) Huntington's disease animal model. Posterior analysis was conducted on mitochondrial biogenetics, oxidative stress, neurobiological behaviors and histopathological assays. It was proven quercetin exhibits protective effects by attenuating mitochondrial oxidative stress (reduced lipid peroxidation and mitochondrial swelling), as well as increasing motor skills and antioxidant elements (Evidence Level 2B) 92 . Additionally, in 2014, quercetin was once again tested on 3-NP-induced HD models, confirming previous results of antioxidant properties and motor coordination increase, along with display of behavioral changes throughlessening of anxiety and isolation;also reducing neuro-inflammatory responses with an increase of astrocyte numbers in core lesions and decreased microglial proliferation (Evidence Level 1D) 93,94 .

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9 IV. Conclusion

Flavonoids have been widely investigated in the past decades and have shown a wide variety of physiological effects, determining a therapeutic potential on innumerous diseases, including neurological pathologies. Their neuroprotective effects are mostly related to anti-oxidant and anti-inflammatory properties; however, specific mechanisms have been reached on both in vitro and in vivo animal models of neurodegenerative diseases. It is quite difficult to assess on whether animal experimentation is most likely to predict human outcomes and toxicity, nonetheless, it is a vital part of scientific research and discovery. Evidence-based medicine analyses such studies in order to foresee favorable outcomes, and although most studies conducted with flavonols are in vitro and animal models of experimentation (Evidence Level 1D/2B and 2C), ARRIVE guidelines offer a tool of assessment, in which the goal is to improve transparency and accuracy of these reports. Our findings on the subject suggest in vitro studies are still the majority of literature references, yet in vivo animal experimentation references seems to be well-constructed(Table 2) and able to provide key results, leading to the possibility of human clinical trials. Despite the lack of human trials with Quercetin, Rutin and Isoquercitrin, other flavonoids have been tested and results show neurological features, providing a glimpse of the therapeutic potential of these compounds. We also suggest Isoquercitrin as a viable option to future experiments, due to its superiority of anti-oxidant and anti-proliferative properties.

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[1] [2]

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LEVEL	THERAPY
1A	Systematic Reviews of Randomized Controlled Trials (RCT)
1B	Individual RCT with narrow Confidence Interval
1C	All or None Studies
1D*	In Vivo Animal Trials
2A	Systematic Reviews of Cohort Studies
2B*	I. Cohort Studies (In Human) II. Ex Vivo Studies
2C*	Outcome Research or Ecological Studies or In Vitro Studies
3A	Systematic Review of Case-Control Studies
3B*	Case-Control Studies or Drug Biological Characteristics Assessment Studies
4*	Case-series and poor quality cohort and case-control studies or Literature Review
5	Expert opinion without explicit critical appraisal

*Modified items from Oxford CEBM

Figure 1: Table 1 :

2

Year 2017

Figure 2: Table 2 :

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