Neuroprotective profile of Piper Methysticum (Kava Kava) and its effects on the Central Nervous System: a systematic review

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Piper Methysticum (kava-kava)
Neuroprotection
Anxiety
Neurodegenerative diseases

Abstract

Introduction: Piper Methysticum is a perennial shrub, native to the Pacific Ocean with historical and cultural significance, described in the literature as a compound that has a positive action on the nervous system, has anxiolytic, sedative, analgesic, anti-inflammatory, anticonvulsant and anti-ischemic effects, having kavalactones as its main component. The aim of this work was to systematically review the effects of Piper Methysticum supplementation on neurological disorders. Materials and Methods: The research was conducted
through the databases PubMed, Science Direct, Cochrane Library, Scopus, Web of Science, Medline via Proquest and Capes Periodicals, through which a quantity of 10 pertinent articles was gathered. **Results:** Piper Methysticum demonstrated significant positive responses to reduce oxidative stress and neuroinflammation in neurodegenerative diseases. In addition, Piper methysticum extract can have anti-ischemic and anticonvulsant effects mediated by blocking the Na+ channel voltage, as well as behavioral changes similar to anxiolytics and significant sedation. **Conclusion:** Thus, considering that Piper methysticum proves to be effective and has a phytotherapeutic potential to act as an adjuvant or alternative to existing drugs.

**Introduction**

Neuroprotection is a relatively new concept in neuroscience research and aims to cover a wide variety of mechanisms, aiming at the preservation and regeneration of cells, structures and functions of the nervous system, as well as the prevention or progression of several neurological disorders (CARROS et al., 2006).

Herbal medicines and their multiple active compounds have scientific relevance in the treatment of neurological disorders, acting effectively in the symptoms of numerous pathologies. In the last decades, interest in natural products has grown significantly, with the expansion of the use of herbal medicines (SACHAN et al., 2015), a recent review by Izzo et al. (2016) reports a 6.8% increase in sales of herbs and dietary supplements in the U.S. in 2014, with an estimated over $6.4 billion in total sales. In addition, about 25% of all drugs prescribed by doctors in current medicine are obtained from herbs in different forms (SAKI et al., 2014).

The concern with the side effects of conventional medicine and the efficiency of medicines derived from new herbs have contributed to the increase in natural products as a substitute for synthetic drugs (DARAKHSHANA et al., 2015). In this context, Piper Methysticum, popularly known as Kava or Kava-kava, is a perennial
A shrub, belonging to the pepper family (Piperaceae), native to the Pacific Ocean with historical and cultural significance, described in the literature as a compound that has neuroprotective action and anxiolytic, sedative, analgesic, anti-inflammatory, anticonvulsant and anti-ischemic effects. Most of these pharmacological effects have been attributed to six kavalactones isolated from kava extracts, including yangonin, kawain and methysticin, dihydromethysticin, dihydrokavain and demethoxyyangonin (SINGH, 1992; TERAZAWA et al., 2013).

Drugs and supplements containing kava extracts are used worldwide, but were withdrawn from the market in 2002 with suspected hepatotoxicity, but in June 2014 the German Federal Institute for Drugs and Medical Devices lifted the previous ban on the use of products of kava. As a European Union regulatory and guidelines body, this change has positive ramifications for the reintegration of kava products, based on empirical evidence in progress from clinical trial research (SAVAGE et al., 2015).

There are many clinical trials on the use of the product kava as an anxiolytic, and a systematic review supports the use of kava for the treatment of generalized anxiety. Other studies have revealed the neuroprotective mechanisms of action of isolated kavalactones (TZENG; LEE, 2015). Sullivan et al. (2009), evaluated the analgesic effect of kava and the results revealed that rats in the kava group remained on the hot plate longer than rats in the control group. In addition, the kava and morphine groups showed very close values, maintaining that kava has analgesic properties similar to that of morphine, even though it does not work at the specific mu receptor.

In view of the promising effects of kava extract on various neurological disorders, with better efficacy, safety and cost-benefit in various pathologies (SAVAGE et al., 2015), the present study aims to analyze the neuroprotective effect of Piper Methysticum in different neurological disorders, based on a systematic literature review.
Materials and Methods

The present study comprises a systematic review of the literature, developed based on stages previously constituted of search, identification, selection and eligibility strategies. The guiding scientific question of the study corresponded to: “Does Piper methysticum have a neuroprotective effect?”

The search strategy in the databases was carried out using the terminologies related to the research, filters and descriptors for articles published in seven databases: PubMed, Science Direct, Cochrane Library, Scopus, Web of Science, Medline via Proquest and Periódicos Capes (Brazilian journal that brings together several international journals).

The search in the databases was carried out from February 2018 to March 2018. The terms used for the research were previously selected considering the controlled vocabulary for indexing articles from the Health Sciences Descriptors (DeCS), through which they were the descriptors “Piper Methysticum” and “Neuroprotective effect” were captured. The Boolean AND operator was applied to promote the combination between the two chosen terms, so that the association “Neuroprotective effect AND Piper Methysticum” was used.

Experimental studies written in English that used Piper methysticum in in vitro or in vivo analyzes were included, evaluating its neuroprotective action, with no time limitation in order to maximize the number of articles related to this subject. The following exclusion criteria were considered: 1) The article is not original; 2) Experimental models other than mice or cell culture; 3) Studies that analyzed the action of Piper methysticum with other compounds, without an isolated group; 4) Absence of a control group (the control group had to be comparable to the group that used Piper methysticum).

Through the initial screening of the studies, using the previously mentioned descriptors, 200 articles were found, of which 8 appeared in the PubMed database, 6 in the Web of Science, 11 in Scopus, 60 in Science Direct, 108
in the Capes Periodicals and 10 in the Medline via Proquest, with no jobs being detected in the Cochrane Library. Then, search filters were used that excluded a total of 150 articles (60 excluded due to duplication, 18 excluded because it was written in languages other than English, 46 excluded due to revisions, 15 book chapters, 1 encyclopedia, 2 conference abstracts, 1 mini review and 7 indexes were excluded), leaving 50 studies on the topic.

After analyzing the titles, 19 articles were excluded and, after reading the summary, another 10 articles were excluded because they were not related to the theme. Thus, 21 articles were read in full. We traced these articles and 11 studies failed in at least 1 criterion: did not test the herbal medicine object of this review, as well as used experimental models other than rats or cell culture and analyzed the action of piper methysticum associated with other compounds, without having isolated group, therefore they were excluded, resulting in a total of 10 articles that were included in the analysis. This systematic procedure that graphically details the selection of studies is demonstrated through a flow chart (Figure 1).

The search for studies was carried out independently by two expert evaluators in the context discussed, using a standard analysis form during all the research strategies mentioned above. There were divergences in the data collected, where their inclusion in the study was conditioned to the consensus between the two evaluators. Language selection was restricted, as only articles published in English were analyzed. The screening of the studies was carried out based on the title and the abstract and, soon after, the publication was fully reviewed and compared.
Figure 1: Flowchart showing the selection process of the articles used in this review. The number of articles shown in this flowchart refers to studies that investigated the neuroprotective effect of Piper Methysticum on the central nervous system found in PubMed, Science direct, Web of Science, Capes Journals, Scopos, Medline (Proquest) and Cochrane.

DATA ANALYSIS

According to Brasil (2012), when the heterogeneity is significant and cannot be explained by any sensitivity analysis, the meta-analysis is not recommended, and the effects of the study’s interventions should only be presented individually.

Therefore, statistical groupings were not considered due to methodological heterogeneities between studies, as the authors evaluated different methods and cell lines, in addition to different dosages of herbal medicine between studies, which justifies the impossibility of carrying out a systematic review with meta-analysis in the data accessed.

RESULTS

As for the main findings and general characteristics, the oldest publication is from 1992 and the 10 articles were published in in-
ternational journals. The studies showed high levels of heterogeneity in important aspects. The search found studies with a possible neuroprotective effect of *Piper methysticum* in different conditions: Neurodegenerative Diseases (DN) (3), Ischemia (3), Anxiety (2) Epilepsy (1), analgesia (1), including different in vivo tests (7), in vitro (3).

The cell models used in the studies vary, PC12 cells were used in (1), BV2 cells (1), Wistar rats (4), Sprague-Dawley rats (1), NMRI and Fischer-344 rats (1), model BALB / cByJ (1) and model C57BL / 6J (1). Regarding the type of compound from *Piper methysticum*, some articles distinguish kava extract (2), methysticin and kavain (1), methysticin (3), kava extract and individual kavapyrones (2), derived from chemically synthesized kavalactones (2).

Different concentrations of solutions prepared with kava extract and its individual constituents ranging from 1 to 220 mg to 1 to 400 μl were used in in vitro and in vivo studies, administered intraperitoneally (ip), orally (vo) and intracelluarly.

As evidenced in the literature, in summary, the reviewed papers demonstrated that *Piper methysticum* has a potential to reduce oxidative stress and neuroinflammation in neurodegenerative diseases through the activation of Nrf2 / ARE signaling. In addition, Kava extract can have anti-ischemic and anticonvulsant effects mediated by blocking the Na+ channel voltage, as well as behavioral changes similar to anxiolytics and significant sedation.

The 10 articles were carefully analyzed and summarized in terms of authorship / year of publication, neuroprotective effect, compound from *Piper methysticum*, experimental model, experimental group / dose regime, tests performed and main findings (table 1).

**Table 1.** A summary of studies on the neuroprotective effect of *Piper Methysticum* in experimental models found in PubMed, Science direct, Web of Science, Capes Journals, Scopos, Medline (Proquest). Databases showing authorship / year of publication, neuroprotective effect, compound from piper methysticum, experimental model, experimental group
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/ dose regimen, tests performed and main findings. ARE, element responsive to antioxidants; APP, amyloid precursor protein; PSEN1, presenilin-1; Nrf2, Nuclear Factor derived from Erythroid 2; μM, micrometer; μG, microgram; iNOS, inducible nitric oxide synthase enzyme; NO, nitric oxide; LPS, Lipopolysaccharide; HO-1, Heme oxygenase-1; NAC, N-acetylcysteine; HPLC, high performance liquid chromatography; GABA-A, type A gamma-aminobutyric acid receptor; V.O, orally; SD, standard deviation; MCA, middle cerebral artery; via I.P., intraperitoneal; MABP, mean arterial pressure; ACSF, Artificial cerebrospinal fluid; DMSO, dimethyl sulfoxide; SLE’s, series of events similar to seizures; 5-HT, 5-Hydroxytryptamine; COPD, dihydroxyphenylacetic acid; HVA, 4-hydroxy-3-methoxy-phenylacetic acid; 5-HIAA, 5-hydroxyindolacetic acid; HPCL-ECD, electrochemical detection coupled to HPLC; mV, millivolts; Hz, hertz.

<table>
<thead>
<tr>
<th>AUTHORSHIP / YEAR OF PUBLICATION</th>
<th>PIPER METHYSTICUM COMPOUND / NEUROPROTECTIVE EFFECT</th>
<th>EXPERIMENTAL MODEL</th>
<th>GROUP REGIME AND EXPERIMENTAL DOSE</th>
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<tr>
<td>Fragoulis et al., 2017</td>
<td>ARE, element responsive to antioxidants; APP, amyloid precursor protein; PSEN1, presenilin-1; Nrf2, Nuclear Factor derived from Erythroid 2; μM, micrometer; μG, microgram; iNOS, inducible nitric oxide synthase enzyme; NO, nitric oxide; LPS, Lipopolysaccharide; HO-1, Heme oxygenase-1; NAC, N-acetylcysteine; HPLC, high performance liquid chromatography; GABA-A, type A gamma-aminobutyric acid receptor; V.O, orally; SD, standard deviation; MCA, middle cerebral artery; via I.P., intraperitoneal; MABP, mean arterial pressure; ACSF, Artificial cerebrospinal fluid; DMSO, dimethyl sulfoxide; SLE’s, series of events similar to seizures; 5-HT, 5-Hydroxytryptamine; COPD, dihydroxyphenylacetic acid; HVA, 4-hydroxy-3-methoxy-phenylacetic acid; 5-HIAA, 5-hydroxyindolacetic acid; HPCL-ECD, electrochemical detection coupled to HPLC; mV, millivolts; Hz, hertz.</td>
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<tr>
<td>Terazawa et al., 2013</td>
<td>Chymically synthesized kavalactone derivative, 2',6' - dichloro -5,6 - dehydro - 4 - hydroxy - 3 - methoxy - phenylacetic acid (Compound 1)</td>
<td>BV2 microglial cells isolated from mixed cultures of neo-cortical cells of C57 / BL6 mice</td>
<td>7 groups: Control (BV2 cells incubated for 1 h in the absence; presence of 10 μM compound 1 (chymically synthesized kavalactone derivative); naturally derived kavalactones (yiangonin, kawain and methysticin), and then treated with or without LPS (1 μg/ml)</td>
<td>Measurement of nitric oxide production; Western blot analysis; Transfection and luciferase assay.</td>
<td>The study suggests that administration of Methysticum activates the NRF2 / ARE system in the hippocampus of mice. It also demonstrated that Methysticum protects AD mice against oxidative stress and associated neuroinflammation due to Nrf2 activation. In addition, Methysticum improves long-term memory impairment in this A3 mouse model. Kavalactones can be suitable candidates to serve as leading compounds for the development of a new class of neuroprotective drugs.</td>
</tr>
<tr>
<td>Tanaka et al., 2012</td>
<td>Kavalactone</td>
<td>PC12 Cells</td>
<td>Experiment 1: PC12 cells transfected</td>
<td>Measurement</td>
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DISCUSSION
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2010

derivative (2', 6'-dichloro-5-methoxy-6-dehydrokawain (E) 6'-2, 6'-dichlorocorystyl) + methoxy-5,6-(methoxy-methyl)-7H-pyrazine-2,3-dione

- Compound 1;
- Protection against oxidative stress
  "in vitro"

with the ARE family luciferase reporter vector and Renilla luciferase control vector were treated with 10 μM yohimbine, kawain, methysticum or compound 1 for 24 h.

Experiment 2: PC12 cells were pretreated for 1 h with NAC (2.5 mM) and then treated for 3 h with compound 1 (10 μM).

Experiment 3: PC12 cells were pretreated for 24 h with or without compound 1 (10 μM) and then treated for 24 h with or without 100 μM H2O2.

Experiment 4: PC12 cells were pretreated for 1 h with PD98059 (20 μM) or SB203580 (5 μM) and then treated for 3 h with 1 (10 μM).

for intracellular ROS levels by using the fluorescent probe CM-H2DCFDA.

-Western blot analysis for HO-1 c b-actin protein;
-Western blot analysis for HO-1 c GCCs; NQO-1 b-actin;
-Western blot analysis for pNp and b-actin;
-Western blot analysis for phosphorylated and total ERK1/2 and p38.

derivatives that are more potent in activating Nrf2 / ARE than natural compounds, a series of chemically modified kavalactones has been synthesized. Among 81 compounds tested, a kavakalactone derivative (compound 1) exhibited stronger potentiating activity than natural kavalactones. In addition, it is suggested that compound 1 protects against oxidative stress and neuronal cell death, as it was considered as preconditining in the activation of Nrf2 / ARE. Thus, the compound has the potential to reduce oxidative stress and improve diseases related to oxidative stress in the brain.

Garrett et al., 2003

Kava extract;
- Acute anxiolytic behavioral changes
  "in vivo"

Isogenic mice BALB/cByJ

Experiment 1: Control groups included vehicle-vehicle and fluoxazin vehicle-vehicle treatments. Test groups included vehicle-diazepam, fluoxazin-diazepam, vehicle-kava and fluoxazin-kava treatments.

Experiment 2: For antagonism experiments in the elevated plus-maze mice were administered 10 mg/kg fluoxazin and an ED10 dose of diazepam (1 mg/kg) or kava (133 mg/kg).

HPLC analysis; Behavioral assaying; Microscopy avoidance assay; Elevated plus-maze assay; Locomotor activity.

It has been demonstrated that Kava extract also caused a profound decrease in locomotor activity (ED10 of 172 mg/kg). Fluoxazin, a competitive benzodiazepine receptor antagonist, blocked both the anxiolytic and sedative effects of diazepam, but had no effect on kava’s behavioral actions. Kava extract produces significant murine anxiolitic-like behavioral changes and sedation that are not mediated through the benzodiazepine binding site on the GABA A receptor complex.

Backlund et al., 1996

Kava extract and its constituents kawain, dihydrokawain, methysticin, dilydromethysticin and yangsianin;
- Protects against ischemic brain damage
  "in vivo"

Mice and mice (NMRI and Fischer-344)

Experiment 1: Kava extract (150 mg/kg) was administered p.o. 1 h before ischemia. The values are given as means ± S.D. of 10 (controls and kava extract) and 10 (kava extract) experiments.

Experiment 2: The infarct area on the mouse brain surface was determined planimetrically 48 h after MCA occlusion. The compounds were administered i.p. 15 min before MCA occlusion. Values are shown as means ± S.D. from 10 (methysticin - 10 and 30 mg/kg), 10 (controls and dilydromethysticin) experiments.

Experiment 3: Ischemia was induced by MCA occlusion. After 48 h, the infarct area on the mouse brain surface was assessed planimetrically. The drug was administered i.p. 30 rain before ischemia. The values are presented as means ± S.D. of 12 (controls) and 13 (loratadine 20 mg/kg) experiments.

Amelior PaO2; PaO2; pH Plasma glucose Arterial blood pressure MABP Temperature Body weight

It has been shown that kava extract, methysticin and dilydromethysticin produced effects similar to those of the reference substance memantine. In addition, kava extract (150 mg / kg, 1 h before ischemia) decreased the area of infarction in mouse brains and the volume of infarction in brain of rats. Methysticin, dilydromethysticin (10 and 30 mg / kg, 15 min before ischemia) and memantine (20 mg / kg, 30 min before ischemia) significantly reduced the area of infarction in the brain of mice. All other compounds did not have a beneficial effect in the area of infarction in the brain's area. Thus, it is suggested that the kava extract exhibited neuroprotective activity, probably mediated by its constituents methysticin and dilydromethysticin.

Schnitz et al., 1995

- Seizure models
  "in vitro"

Sections of the temporal cortex containing the hippocampus and entorhinal cortex of Wistar rats

The experiments were performed on 8-10 transverse temporal lobes slices containing the neocortical areas T2 and T3, the temporal cortex, the entorhinal cortex (EC), the hippocampus formation with the dentate zone, areas CA3 to CA1 and the

Electrophographic

It can be seen that methysticin in concentrations ranging from 10 to 100 μM blocked all types of epileptiform discharges induced in our experiments, discharge stimulus-induced explosions at low Me+ ++ +, all types of low recurrent activity induced by Me+ ++ +.
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<table>
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<th>Study</th>
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<td>Baum et al., 1995</td>
<td>Kava extract and individual Kavalactones; Levels of neurotransmitters in the nucleus accumbens</td>
<td>Male Wistar rats</td>
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<td>Magura et al., 1998</td>
<td>(+) - Methysticin; Changes in neuron excitability in a focal ischemia model</td>
<td>Wistar rats and mice</td>
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<tr>
<td>Magura et al., 1997</td>
<td>(+) Methysticin and (+) - Kavain; Inhibition of Na (+) channels operated by voltage in the neurons of the hippocampus CA1 of rats.</td>
<td>Wistar rats</td>
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</table>
Neuroprotection is a relatively new concept in neuroscience research and is intended to cover a wide variety of mechanisms, aimed at the preservation and regeneration of cells, structures and functions of the nervous system, as well as the prevention or progression of several neurological disorders (CARRO et al., 2006). The consequences and social and economic impacts generated by these neurological pathologies establish an important study theme, as it is necessary to elucidate their mechanisms and search for natural medicines that act in the repair of damage and sequelae, resulting in decreased degeneration, neuronal and a better quality of life.

As reported, herbal medicines and their multiple active compounds have scientific relevance in the treatment of neurological disorders, acting effectively in the symptomatology of these pathologies. In this context, we investigated the neuroprotective effect of Piper Methysticum, a perennial shrub, native to the Pacific Ocean with historical and cultural significance, described in the literature as a compound that has a positive action on the nervous system, due to the action of its active properties capable of acting in the repair of experimental damage in pathologies such as Alzheimer’s disease (AD), cerebral ischemia, convolution and anxiety, as evidenced in the systematic search (TERAZAWA et al., 2013).
Neurodegenerative Diseases Alzheimer’s disease (AD) is a neurodegenerative pathology that results in progressive loss of function, structure and number of cells, leading to generalized atrophy of the brain and profound cognitive and behavioral deficit (RODRÍGUEZ; VERKHRATSKY, 2011). Histopathologically it is characterized by accumulation of beta-amyloid peptide (βA), which can initiate a cascade of oxidative events and chronic inflammation, causing neuronal death (WRUCK et al., 2008).

Several studies represented in table 1 investigate the action of Piper methysticum in experimental models of neurodegenerative diseases and, specifically, in AD, demonstrating the neuroprotective effect of this herbal medicine (FRAGOULIS et al., 2017; TANAKA et al., 2010; GARRETT et al., 2003). Recent studies, such as that by Fragoulis et al. (2017), show that one of the possible explanations for the mechanism of action of piper in AD is associated with the activation of the erythropoi-d2-related nuclear factor (Nrf2).

Nrf2 is the main regulator of detoxifying / antioxidant enzymes phase II, including heme oxygenase 1 (HO-1).

The transcription factor Nrf2 binds to ARE (antioxidant response element), transcribing a battery of genes involved in redox status, anti-inflammatory response and detoxification (JOSHI; JOHNSON, 2012). A study by Lobota et al. (2016), reports that the activation of Nrf2 and the induction of HO-1 are involved in the regulation of inflammation.

Fragoulis et al. (2017), investigated the action of Methysticin extract - one of the main kavalactones - in doubly transgenic mice with prominent AD pathology, considering that the rats co-express the mutated human beta amyloid precursor protein (APP) and the mutated human presenilin 1 (Psen1). The study administered Methysticin by oral gavage, once a week, for a period of 27 weeks in adult rats and evaluated the action of Methysticin in the concentration of 6mg / kg through the tests Open field, Histology and Immunohistochemistry, Oxyblot, ELISA Aβ, Multi-plex luminex Assay, Y-la-
byrinth, Morris Aquatic Labyrinth (LAM).

The result of this study showed that the oral administration of 6mg / kg of Methysticin significantly increased long-term memory in the middle age of APP / Psen1 mice, inducing cytoprotective factor Nrf2 transcription. In this way, oxidative damage and associated neuroinflammation were reduced.

The authors concluded that Methysticin works as an indirect antioxidant, since it can activate the antioxidant, anti-inflammatory and cytoprotective pathway of Nrf2. In addition, it appears to have considerable potential for clinical application in the prevention and therapy of AD, serving as a leading framework in the design of a new class of drugs for the treatment of neurodegenerative diseases (FRAGOULIS et al., 2017).

Another study developed with the purpose of looking for agents that activate the Nrf2 factor was carried out and three analytically pure kavalactones - Methysticin, Yangonin and Kavain - were researched. The effects of kavalactones on the protection of neural cells against beta-amyloid peptide-induced neurotoxicity (βA) were evaluated using the ARE-luciferase and Western blot assays.

The results indicated that the kavalactones Methysticin, Yangonin and Kavain activate Nrf2 / ARE dependent on time and dose in the neural C6 PC-12 and C6 astroglial cells and, therefore, positively regulate the cytoprotective genes. At the same time, viability and cytotoxicity tests have shown that the activation of Nrf2 is able to protect neuronal cells from neurotoxicity, attenuating neuronal cell death caused by β amyloid (WRUCK et al., 2008).

As mentioned, one of the main characteristics that can contribute to the evolution of neurodegenerative diseases is the accumulation of β-amyloid peptide (Aβ), which potentiates a cascade of oxidative events, damaging several highly reactive biomolecules, including DNA, carbohydrates, proteins, acids nucleic acids and lipids, leading to cell dysfunction and apoptosis (WRUCK et al., 2008; BIRBEN et al., 2012).

Oxidative stress is defined as an imbalance in cellular antio-
oxidant defense systems and reactive oxygen species (ROS), occurring when excess oxygen radicals are produced in cells, generating the accumulation of these ROS and, consequently, overloading the normal antioxidant capacity (GAGNÉ, 2006; EMERIT; EDEAS; BICAIRE, 2004). Most ROS are produced by living organisms as a result of the usual cellular metabolism, generated during respiration in the mitochondria. In low to moderate concentrations, they play physiological roles, however, in high concentrations, they produce adverse changes in cellular components (STADTMAN, 2004). Hydrogen Peroxide (H2O2) is one of the main ROS and an inducer of cellular oxidative stress (HALLIWELL, 2012; DASURI; ZHANG; KELLER, 2013).

Given the pathogenic impact of oxidative stress and neuroinflammation, therapeutic strategies in order to mitigate these processes are considered an effective way of providing neuroprotection (VAN MUISWINKEL; KUIPERIJ, 2005). Many plants are considered a rich source of antioxidants, since they inhibit or delay oxidative degradation (WUL et al., 2002), researched six biologically active compounds from the roots of Piper methysticum (kava kava), to evaluate the inhibitory potential of cyclooxygenase and antioxidant effects. The results indicated that Dihydrokawain and yangonin showed higher concentrations of COX-I and inhibitory activities of COX-II. In addition, yangonin and methysticim showed moderate antioxidant activity in the free radical scavenging test.

On the other hand, the work conducted by Tananka et al. (2010) shows that chemically modified kavalactones also have the potential to increase cellular antioxidant capacity and improve diseases related to oxidative stress. Among the 81 compounds tested, a kavalactone derivative, named compound, exhibited stronger ARE enhancing activity and the induction of the HO-1 protein was superior to that of natural kavalactones.

One of the mechanisms that elucidate this finding is the action of compound¹ in potentiating the cellular defense system, activa-
ting, after nuclear translocation, the Nrf2 / ARE pathway inducing the expression of several phase II enzymes (GPX, γ-GCS and HO-1), increasing the levels of intracellular ROS, protecting against PC12 cell death induced by oxidative stress by increasing the expression of HO-1 (TANANKA et al., 2010). The study by Van Muiswinkel and Kuiperij (2005) also corroborates this evidence, showing that the activation of Nrf2 signaling attenuates oxidative stress in neurodegenerative diseases through the induction of phase II antioxidant enzymes such as HO-1.

Another study carried out later by Terazawa et al. (2013), demonstrated that a chemically synthesized kavalactone derivative, compound 1, can reduce neuroinflammation, as well as oxidative stress in BV2 microglial cells. These effects were attributed to the ability of compound 1 to inhibit lipopolysaccharide (LPS) stimulated iNOS induction and nitric oxide (NO) production via activation of Nrf2 signaling and induction of heme oxygenase 1 (HO-1). Therefore, for the study in question, compound 1, through the activation of Nrf2 signaling, has the potential to increase expression and antioxidant activity, decreasing ROS levels and cytotoxicity, exhibiting cell viability.

Taken together, it is understood that the Nrf2 / ARE signaling pathway is an attractive therapeutic target for neurodegenerative diseases and that chemically modified kavalactones, as well as naturally occurring kavalactones, can mitigate neurological damage, reducing oxidative stress and neuroinflammation.

Anxiety

Anxiety is a diffuse mental condition, manifested through unpleasant sensations of fear and apprehension without a specific cause (SINGH; SINGH, 2002). Brief moments of anxiety are common in everyday life and do not guarantee treatment. However, when it is felt intensely and persistently and the individual has little or no control over the situation, it is diagnosed as anxiety disorders (SAKI et al., 2014; STRESS, 2016). Anxiety disorders present cognitive, somatic, physical and
emotional symptoms, including insomnia, restlessness, nervousness/irritability, fatigue, concentration difficulties and muscle tension (AMERICAN ASSOCIATION OF PSYCHIATRY, 2013).

Currently, the psychotherapeutic alternative chosen to treat patients is through antidepressant drugs, such as selective serotonin and serotonin-norepinephrine reuptake inhibitors (ISRS-SNRI), tricyclic antidepressants and benzodiazepines (BANDELOW et al., 2013). However, due to the undesirable and destructive side effects of these drugs, including drowsiness, cognitive impairments and symptoms of dependence and withdrawal, many patients prefer herbal options. Several plants with anxiolytic activity have been studied in clinical trials, and Kava (Piper methysticum) is shown to be effective, being mentioned as a non-addictive, non-hypnotic anxiolytic, with phytotherapeutic potential to act as an adjunct or alternative to anxiolytic drugs existing (SAKI et al., 2014; SAVAGE et al., 2015).

A meta-analysis review by Pittler et al. (2010) evaluated the effectiveness and safety of kava extract versus placebo for the treatment of anxiety. Seven randomized controlled trials using Piper methysticum indicated that kava extract is superior to placebo and relatively safe as a treatment option for anxiety.

Another recent meta-analysis, conducted by Ooi et al. (2018), revealed similar results, mentioning that there is promising evidence from well-designed clinical studies suggesting Kava, particularly aqueous extracts, as an effective treatment for generalized anxiety disorder (GAD). The authors add that the effect of Kava is comparable to the pharmacological drugs normally prescribed (buspirone and opipramol), but with less adverse consequences.

Corroborating the aforementioned study, Boerner et al. (2003), conducted a multicenter, double-blind, randomized clinical trial with 129 outpatients and investigated whether the extract of Kava-Kava LI 150 is as effective as Opipramol and Buspirone in TAG. The subjects received 400 mg of Kava LI 150, 10 mg of Buspirone or 100 mg of Opipra-
mol daily for 8 weeks. The results showed that in 127 patients, no significant differences were observed in relation to medications and, therefore, Kava-Kava LI150 is well tolerated and as effective as Buspirone and Opipramol.

The therapeutic properties of kava are supported by the six main kavalactones (dihydromethysticin, kavain, dihydrokavain, methysticin, yangonin and demethoxyyangonin), of which kawain and dihydrokawain have more intense anxiolytic activity (WUL et al., 2002). Current evidence indicates that kavalactones play their role.

The from specific actions postulated on the gamma-aminobutyric acid (GABA) pathway, including blocking voltage-gated sodium ion channels, greater ligand binding to type A GABA receptors, decreased release of excitatory neurotransmitters due to calcium channel, reduced neuronal reuptake of norepinephrine (norepinephrine), reversible inhibition of monoamine oxidase B and cyclooxygenase. However, the pathophysiology of anxiety and the neurobiological actions that support the anxiolytic effects of Kava extract and kavapyrones are not so clear yet and need more information to be elucidated (SAVAGE et al., 2015; CAIRNEY; MARUFF; CLOUGH, 2002; DINH et al., 2001; SAVAGE et al., 2018).

Baum, Hill and Rommelspacher (1998) developed a study with the purpose of knowing the effects of kava extract and individual kavapyrones on the mesolimbic reward system, specifically, on the levels of neurotransmitters in the nucleus accumbens, through in vivo microdialysis. After intraperitoneal (ip) administration of kava extract and kavapyronas in male rats, the levels of dopamine, 5-hydroxytryptamine (5-HT) and some of its metabolites changed, causing feelings of relaxation, drowsiness and euphoria (depending on the dosage). The authors proved that a small dose of kava extract (20 mg / kg ip) caused changes in the behavior of the rat (relaxation), activated dopaminergic neurons and the mesolimbic dopaminergic reward system, the effects remaining for several hours due to the lipophilic properties...
of the active compound of the extract (OOI et al., 2018).

In this study, it can also be shown that the minor components of kava extract cause pharmacological effects. Kavalactones D, O L-kawain induced a decrease in dopamine levels (low doses) and an increase or no change in dopamine concentrations (larger doses). Yangonin caused a decrease in dopamine levels, reducing the activity of dopaminergic neurons. Desmethoxyyangonin an increased levels of dopamine. Dihydrokawain, methysticin and dihydromethysticin did not show significant effects. Other findings of the present study were changes in the concentrations of 5HT after administration of kava extract or individual kavapyronas. About half of the rats had increased levels of 5-HT after the action of kava extract and, this effect, can explain the sleep-inducing action (BAUM; HILL; ROMMELSPACHER, 1998).

In their analysis Garrett et al. (2003) systematically evaluated the anxiolytic and sedative effects dependent on the acute dose of kava extract in quantitative behavioral tests in mice and compared behavioral changes induced by kava and diazepam. The research findings demonstrate that the increase in kava dose caused a reduction in locomotor activity, revealing that kava has dose-dependent anxiolytic properties in both behavioral tests, another factor to be considered in the study is that flumazenil blocked the anxiolytic effects, and diazepam sedatives, but had no effect on kava’s behavioral actions. In addition, it has been shown that Kava extracts produce significant behavioral changes similar to anxiolytics and significant sedation that are not mediated through the benzodiazepine binding site in the GABAA receptor complex. The mechanisms proposed for the aforementioned study, referring to the anxiolytic and sedative action of these constituents, are represented in Figure 2.
Extract to control anxiety and sedation. Kava extracts produce significant behavioral changes similar to anxiolytics and significant sedation that are not mediated through the benzodiazepine binding site in the GABA-A receptor complex. Further studies are needed, however the results obtained provide a means to begin to determine which of the kavalactones and kava extracts are responsible for the anxiety-reducing effects and whether the anxiolytic and sedative effects can be separated from each other.

A pioneering study developed by Chua et al. (2016) evaluated the functional characteristics of Kavain and the molecular mechanism of γ-aminobutyric acid type A receptors (GABAA Rs), in order to understand the mechanism of action between molecular targets and psychoactive agents, seeking experimental evidence to support to this direct interaction (Kavain and the GABAA receptors). The results showed that kavain positively modulated all GABAA receptors regardless of composition, but the action of increasing kavain Rs GABAA (300 μM) was not affected by flumazenil and this insensitivity to flumazenil indicates a non-benzodiazepine mechanism of the studied kavalactone. This finding corroborates with other studies that failed to detect any significant interaction of kavalactones with the benzodiazepine site (GARRET et al., 2003; DAVIES et al., 1992).

Cerebrovascular diseases

Cerebral ischemia consists of a decrease in cerebral blood flow in an area of the brain, making it insufficient to meet its metabolic demands, leading to hypoxia and neuronal death may occur when the reduction in blood supply is persistent and severe (SCHREIHOFER, 2015; BRUCE, 2007). As a consequence of ischemia, epileptic seizures can be triggered, generating brain damage and greater severity of the clinical picture, since the glutamate and aspartate channels are activated, excessively releasing these neurotransmitters and, subsequently, NMDA receptors (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) are triggered causing the influx of calcium, sodium and water in the cells of the injured region, causing excito-
toxicity mediated by free radicals, deficit neurological and apoptosis (PATEL, 2008; LEKER; NEUFELDB, 2003).

The endogenous mechanisms of self-protection activated after brain damage are very similar in cerebral ischemia and epilepsy. Thus, the drugs that are successful in the treatment to mitigate the brain damage induced by seizures can also be useful to minimize ischemic injury (LEKER; NEUFELDB, 2003). Thus, Piper Methysticum is cited as a multi-potent phytopharmaceutical, due to its numerous pharmacological effects that include anxiolytic, sedative, anticonvulsant, anti-ischemic, local anesthetic, anti-inflammatory and analgesic activities. Therefore, the use of Kava in brain disorders can present important clinical and financial advantages, acting as an adjunct or alternative to existing drugs (SINGH, 1992).

This evidence is demonstrated through the experimental study developed by Backhauss and Krieglstein (1992) that induced focal cerebral ischemia in rodents through microbipolar coagulation of the left middle cerebral artery (MCA), with the objective of evaluating whether the kava extract and its constituents kawain, dihydrokawain, methysticin, dihydromethysticin and yangonin are able to reduce the size of a heart attack zone in rats and mice, providing protection against ischemic brain damage. The compounds were administered ip, except for dekava extract, which was administered orally. The results showed that Kava extract decreased the infarction area in mouse brains and the infarction volume in rat brains, methysticin and dihydromethysticin significantly reduced the area of infarction in the brain of mice, as shown in Figure 3, showing Thus, the neuroprotective activity of Kava extract through the action of the constituents methysticin and dihydromethysticin. The other Kavapyronas failed to produce a beneficial effect in the area of infarction.

In the ischemic process, an extremely relevant event for the expansion of brain injuries is the massive rupture of ionic homeostasis (LEKER; NEUFELDB, 2003).
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Figure 3: Main mechanisms of action of Kava Extract and its constituents Kawain, dihydrokawain, methysticin, dihydromethysticin and yangonin. The positive mechanisms of action of Kava extract and its constituents were observed in the treatment of an experimental model of cerebral ischemia induced by microbipolar coagulation of the left middle cerebral artery and it was found that kava extract at a dose of 150mg / kg reduces the area of infarction in mouse brains and the volume of infarction in mouse brains. Methysticin and dihydromethysticin at doses of 10 and 30mg / kg significantly reduced the area of infarction in the brain of mice.

High calcium concentrations can cause an increase in cellular oxidative stress that contributes to cell damage, as well as the activation of various enzymes such as lipases, proteases and endonucleases, which can damage DNA, cell proteins and lipids, leading to apoptosis , activation of enzymes, such as neuronal nitric oxide synthase, which generate toxic free radicals, and activation of arachidonic acid metabolism, which promotes cerebral edema. The interruption of ionic homeostasis plays an important role in maintaining the main physiological mechanisms and, consequently, in cell viability, reducing cell damage in neurological pathologies (URENJAK; OBRENOVITCH, 1996; SINGH, 1992).

Magura et al. (1998) developed a research in order to know the effects of Kavalactone (+) – Methysticin on the mechanisms responsible for the inactivation of the sodium channel in neurons of the hippocampal zone CA1 in the brains of rats. The study found that the action of Methysticin (100 μM) considerably accelerated the inactivation process, as long as the membrane potential was within the range of -80 to -20mV. However, when depolarization was increased, Methysticin’s influence on the rate of inactivation became much less. The authors concluded that the effect of methysticin on inactivation kinetics results in consi-
derable changes in the excitability of neurons, this is probably behind the neuroprotective effects of this drug.

Another study previously carried out by the aforementi-

ed author showed that synthetic Kavapyrones, (+) - methysticin and (+/-) - kavain, inhibit the Na + channels in the central neurons of rats leading to decreased excitability (Figure 4), a property that equivalent to Na + channel blockers such as lidocaine, phenytoin and flunarizine, which inhibit excess Na + influx present in many neurological disorders (BRUCE, 2007). In addition, Methysticin was about four to five times more potent blocker at the peak amplitude of Na (+) currents than (+) - kavain and both delayed recovery from inactivation. Therefore, the anti-ischemic and anticonvulsant effects of kava ingredients can be partly mediated by blocking the Na + voltage and by the interaction of (+) - metastin and (+/-) - kavain with the states of Na (+) - closed and inactivated at rest (MAGURA et al., 1997).

![Figure 4: Mechanisms of action of Kava, Methysticin and Kavain Extract in inhibiting Na (+) channels.](image)

The actions of antiepileptic drugs (AEDs) generally target the onset and spread of seizure activity, whereas neuroprotective therapies aim to antagonize damage-promoting mechanisms and strengthen self-protection pathways in an attempt to prevent cells at risk from dying. In the case of epileptic brain injury, the prevention of new seizure activities is an established goal for neuroprotection (CHUA et al, 2016). Methysticin
is one of the constituents of Piper methysticum that has anticonvulsant and neuroprotective properties (SINGH, 1992).

In their analysis Schmitz et al. (1995), evaluated the effects of methysticin in three different in vitro models of epileptiform activity in slices of the hippocampus and entorhinal cortex of rats. The first model explores the fact that seizures are associated with increases in [K +], the second analyzes the low Ca2 + induction in the CA1 area and the third assesses the low Mg 2+ induction. In addition, the effect of methysticin on the concentration of extracellular Ca 2 + was also investigated. As a result of such spontaneous manipulations, the research points out that the elevation of [K +] induced crisis-like events with tonic and clonic electrographic phases in the CA1 area, when the [Ca2 +] induction decreased, causing recurrent crises with major changes in potential negative field and the reduction of Mg2 + induced short recurrent discharges in the CA3 and CA1 areas. However, epileptiform discharges develop in most brain structures, including the hippocampus and the entorhinal cortex.

Other results found in the aforementioned study indicate that methysticin reversibly blocked all these types of epileptiform activity, in a concentration range of 10 to 100 μM. Therefore, the authors suggest the development of antiepileptic drugs based on methysticin, since the activity profile of methysticin in controlling a series of seizure-like events (SLE’s) is broader than standard antiepileptic drugs (SCHMITZ et al., 1995).

**CONCLUSION**

This systematic review provides evidence that the administration of Piper Methysticum and its isolated active compounds are effective in in vivo and in vitro models of neurological diseases, acting mainly as anxiolytics, sedatives, analgesics, anti-inflammatories, anticonvulsants and anti-ischems, helping several neurochemical and behavioral mechanisms present in these pathologies. Thus, it can be seen that the mechanisms presented by Piper Methysticum offer a futu-
re alternative for the treatment of these pathologies, going beyond the capacity presented by conventional medicine, with less adverse effects and important clinical and financial advantages. However, it is suggested that further research be conducted to better elucidate and understand the mechanism of action of the bioactive agents composed in this plant, since it proves to be effective and with a phytotherapeutic potential to act as an adjuvant or alternative to existing drugs.

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Conflicts of interest

There are no conflicts of interest.


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